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OBSERVATIONS ON BREECH PRESENTATION AND DELIVERY

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THIS paper represents a four-years study of 218 single breech deliveries at St. David's Hospital. The corrected foetal loss was two stillbirths, both in parous patients, in babies weighing 3 pounds 10 ounces and over in a corrected series of 165 cases—an incidence of 1·2 per cent. Six cases of prolapse of the cord are included. The Caesarean section rate was 16 per cent. Eighty per cent of the cases (92 per cent in the corrected series) were booked cases in that they attended the antenatal clinics in the area.

The period chosen, from 1st April, 1954 till 31st March, 1958, represents the official life span of the writer in his capacity of Senior Registrar at the hospital. It also represents the first period in his training, during which he had a long enough interval to devote to a subject which, to him, has always been of primary interest. During the period he was privileged to act as a member of a team representing the obstetric unit of the St. David's Hospital. The results represent the co-operative participation of all members of the team from the Senior Consultant to the most junior midwife on duty, with the active co-operation of the General Practitioners and District Midwives in the area, in a system which advocates:

(1) Reference to and delivery of all breech presentations in hospital.
(2) Careful prenatal assessment of cases.
(3) Expectant supervision of all cases in labour.
(4) Experienced obstetrical supervision of all breech deliveries.
(5) The teaching of house-surgeons and the application in practice of the principle that a knowledge of various methods for the delivery of the arms and after-coming head is safer than the knowledge of one method only carried out as a routine.
(6) Insistence on at least two members of the resident staff and, if possible, a paediatrician being called and attending each breech delivery.
(7) The delivery of the baby being carried out as quickly as possible consistent with the avoidance of traumatic injury to the foetus and mother, as soon as the buttocks have been delivered by the mother's effort.
(8) The employment of a wide episiotomy.
(9) Readiness to carry out Caesarean section on:
   (*a*) Babies above 7½ pounds if there is any doubt about the pelvic-foetal relationship but believing in and practising "trial labour".
   (*b*) Labours exhibiting inco-ordinate uterine action.

Cox (1950) states that 3 to 5 per cent corrected foetal loss should be a good result for any teaching hospital in view of the varying medical personnel that has to be instructed in the art of breech delivery. That this need not be so is illustrated by the St. David's figures. Seventy-six per cent of the vaginal breech deliveries at the hospital were carried out by a changing resident obstetrical and gynaecological staff of two Senior House Officers and one (usually pre-registration) House Surgeon.

Although it is advocated that all breech deliveries by the junior staff should be attended by a more senior member of the staff this obviously has not been always possible in practice because of other duties and maintenance

TABLE I

Author	Hospital	No. of Cases After Correction for Complications	Weight Range	Corrected Foetal Loss Per cent	Deaths Due to Prolapse of Cord	Technique	Caesarean Section Rate Per cent	Percentages of Cases Extracted	Remarks
Calkins (1955)	University Kansas Medical Centre	588 568 403	1,000 g.+ 1,500 g.+ 2,500 g.+	4·0 3·5 2·2	4 (included)	"Assisted breech"	Not reported	Not reported	
Goethals (1955)	Boston Lying-in	228	2,500 g.+	0·9	6 (excluded)	"Assisted breech" Ether anaesthesia	Not reported	Not reported	
Johnson *et al.* (1956)	Mount Hamilton	593 177 (personal)	5 lb.+	0·95 1·9	Cases excluded but number not reported	Extraction Ether anaesthesia	Not reported	75 100	Only cases delivered vaginally reported.
Dieckmann and Harrod (1955)	Chicago Lying-in	942 910 754	1,000 g.+ 1,500 g.+ "Mature"	3·2 1·4 0·92	6 (excluded)	"Manual Aid" (assisted breech)	11·9	43·2	
Cox (1955)	Liverpool Maternity	249	4 lb. 9 oz.+	2·41	1 (excluded)	"Assisted breech" Pentothal anaesthesia	12	Not specified	
Kaltreider (1957)	University of Maryland	634	2,500 g.	2·3	Not specified	Not specified	11	Not specified	
Cutts and Abbas (1951)	Simpson Memorial	867 (total cases)	5 lb. 8 oz.+	2·9 (of total)	5 (excluded)	"Hands off the breech"	10·9	10	(1) Twins included. (2) Percentages expressed as of total number of cases.
Macafee (1956)	Royal Maternity, Belfast	85 83 (private)	Not specified	5·8 1·2	None reported	Not specified	8·2 20·4	Not specified	
Law (1955)	University College	100	1,500 g.+	1·0	None reported	"Assisted breech" General anaesthesia	16	8 5	
Daley and Michael (1953)	St. Helier	283	5 lb. 8 oz.+	5·3	4 (included)	"Assisted breech" Pudendal block	8·1	Not specified	Figures corrected from text of paper.
Hay (1959)	St. David's	165	3 lb. 10 oz.+	1·2	0	"Assisted breech"	16	18	

of off-duty and holiday routine. In 24 per cent of cases the resident staff carried out the delivery without supervision but, for the most part, the cases had already been seen and assessed, either prenatally or in labour by members of the senior staff and the ability of the delivering attendants was known. In all, 82 per cent of the cases were seen by the writer either just before the onset of labour, in labour, or at delivery. Attendance at delivery was achieved in 76 per cent of the total vaginal deliveries. Deliveries which prenatally were assessed as likely to be difficult or unusual were given precedence. In only 20 per cent of the total vaginal deliveries was it necessary for the writer either to take over or to carry out the delivery. The majority of these were of the full extraction type of delivery, the nature of which will be defined below. In all, 60 per cent of the total breech extractions were completed or carried out by the writer.

In the last ten years there has been a dramatic fall in the incidence of foetal loss in breech presentation (Table I). Previously 12 per cent foetal mortality was an accepted loss for British hospitals (Bourne and Williams, 1945). In this country the Liverpool school has led the way in achieving this reduction of foetal loss and it would be difficult to improve upon the excellent results reported by Cox (1950, 1955, 1957) for a large series of cases. The presented series is an attempt to apply the teaching of the Liverpool school to a non-teaching hospital where staffing problems have not always been so easy to overcome as in teaching hospitals. Where we have been lacking in numbers we have gained by our diligence of observation of cases in labour and by our co-operation as a team. Both losses in the series can be traced directly to the point where the principles of team work or careful observation of the patient in labour were not observed. In one case, at the beginning of the series, a house surgeon failed to inform another member of the team and launched on a multigravid breech delivery unaided. He had difficulty with the after-coming head and the baby died of asphyxia. In the other case, in 1956, because of lack of staff in the labour ward, it was impossible to give another multigravid patient the close attention she required and the baby died of asphyxia before it could be rescued. These infants weighed respectively 6 pounds 8 ounces and 8 pounds 15 ounces.

It is realized that the Bangor figures are small in comparison with others but they have been obtained over an extended period of time, and with continued perseverance in the application of our principles they should be maintained.

Cox (1950) has already described the method of delivery of the breech as employed at Liverpool, but as there are some basic differences in interpretation and execution from the Liverpool teaching, as applied to St. David's Hospital, I think it would be beneficial to repeat them in some detail. The principles have already been outlined above.

Careful Prenatal Assessment of Cases

In the prenatal period external cephalic version is attempted with gentleness, without anaesthesia, from the 32nd week in primigravidae and the 34th week in multigravidae. If the baby "does not want to turn" it is "left to nature". In most cases it will have turned when the patient is next seen. If the breech presentation persists at 37 weeks it is unlikely that the condition will change but spontaneous version may still occur up to term (Vartan, 1945). At 37 weeks it is safer to assume that the breech will persist and the case should be assessed as to its suitability for vaginal delivery. In the absence of other limiting factors, such as age, obstetric history, and the presence or absence of other obstetric complications, the question is asked: "Will this baby go easily through this pelvis?" The emphasis here is on the word easily. The assessment of the case involves in most instances (*a*) an accurate clinical assessment of the bony pelvic dimensions and (*b*) estimation of the size of the baby. Since it is quite impossible to assess in advance the cephalo-pelvic relationship without resorting to dangerous and unnecessary X-ray cephalometry a wide margin of safety is aimed at (*vide infra*).

Clinical assessment of the bony pelvis can be carried out with practice sufficiently accurately by digital exploration without resorting to X-ray pelvimetry. Only 18 cases in the St. David's figures had an X-ray pelvimetry assessment

carried out. When in doubt, or when the pelvic inlet shape is in doubt, or when the patient is unco-operative or difficult to examine, it is perhaps safer to resort to X-ray diagnosis. However, one has to consider the dangers of X-ray investigation to the unborn foetus. The methods of clinically examining the pelvis are well known and will not be reiterated. Each obstetrician has his own method of estimating a pelvis. This has been developed by him by experience, and is mostly dependent on his own hand size. The writer would only seek to emphasize certain factors which he has found more important than others. Outlet contraction is more dangerous to delivery of the breech than a similar degree of contraction with a baby of comparable size, presenting by the vertex. In estimating the size of the outlet the length of the sacro-spinous ligament is not so dependable as the length of the sub-pubic coccygeal diameter (the antero-posterior diameter of the outlet). This should not be less than 4½ inches on the examining fingers when a baby of more than 7½ pounds is presenting. The sub-pubic angle and the bi-ischial diameter of the outlet are usually easy to assess but they are of less importance because they rarely exhibit contraction characteristics.

In judging the size of the baby prenatally Kaltreider (1957) takes the mean of four observers' estimations but this should not be necessary. With practice, it is amazing how nearly one can estimate the actual size of the foetus. It is usually easy enough to estimate whether the baby is above or below 7½ pounds, and this is most important since Cox (1950) has shown the death rate in breech delivery of babies above 7½ pounds rises rapidly. With practice, too, the size of the baby as estimated by X-ray can be helpful provided the picture is always taken in the postero-anterior position.

Babies estimated as below 7 pounds rarely present a problem because it is unusual to find a contraction of the pelvis gross enough to make one decide to do a Caesarean section. On the other hand, one should look for the reason for not doing a Caesarean section with babies estimated as over 7½ pounds. The following are the working rules on which to base one's judgment:

(*a*) If pelvis capacious (i.e., diagonal conjugate greater than 4½ inches and outlet good) and baby estimated at 7½ to 9 pounds then vaginal delivery should be safe.

(*b*) If promontory reached at less than 4½ inches and baby estimated as above 7½ pounds do a Caesarean section.

(*c*) If pelvis capacious and baby possibly 9 pounds or more or if pelvis borderline (4½ inches diagonal conjugate) and baby around 7½ pounds and the obstetrician favours a vaginal delivery, then it is quite a feasible procedure to allow the patient to come into labour and conduct a "trial of labour" (*vide infra*).

(*d*) Where the baby is definitely large and can be assessed at more than 9 pounds without any doubt in the obstetrician's mind, it is always wiser to carry out an elective Caesarean section irrespective of the size of the pelvis (Marshall, 1949; Cox, 1950). As Cox (1950) points out it is the size of the body in these big babies which gives rise to difficulty in carrying out the obstetric manœuvres necessary for safe delivery.

Where the obstetrician is in doubt about the pelvic-foetal relationship, or where he is not certain of the ability of the obstetric staff to carry out the breech delivery in his absence, it is probably safer to resort to elective Caesarean section. This statement is based on the Bangor results for Caesarean section, which indicate that it is safer for the foetus when it presents as a breech to be delivered by Caesarean section than by the vaginal route (*vide infra*).

A further foetal variant which might be advocated at this stage as an indication for Caesarean section in borderline cases is the presence of flexed legs. It has come to light forcibly since the figures for this paper were collected that it is definitely more dangerous for the foetus to present by the breech with the legs flexed or even with one leg flexed than it is to have both legs extended (*vide infra*).

The previous obstetric history of the parous patient is not allowed to influence the obstetrician to the extent that he omits to carry out a pelvic assessment. It is realized that the occasional parous patient, with a history of

easy deliveries of big babies presenting by the vertex, has a contracted pelvis. The combination of co-ordinate pains with head moulding has produced easy deliveries and hence a false impression of safety. There is no time for moulding of the after-coming head in a breech delivery.

Expectant Supervision of Cases in Labour

Labour is allowed to proceed in the normal fashion. The extended breech is usually, like the comparable vertex, found to be engaged or fixed in the pelvic brim at the onset of labour and there is little danger of the cord prolapsing. The flexed breech, as a rule, stays high and may do so until full dilation of the cervix with its attendant danger of prolapse of the cord (*vide infra*). It is important to carry out a vaginal examination in all cases of breech presentation when the breech is not engaged in the pelvis at the onset of labour, and in cases where the position of the legs is in doubt. In cases where the legs are flexed, if the cervix is sufficiently dilated to admit two fingers, it is important to feel through the membranes and forewaters whether a cord is lurking high up between the foetal legs. If there is doubt it is safer to rupture the forewaters artificially and make sure. By observing this principle the writer has on two occasions (not in this series) avoided a prolapse of the cord later in labour, by proceeding to immediate Caesarean section. Certainly a vaginal examination should be carried out at once as a routine procedure when the membranes rupture spontaneously in those cases which have not been previously examined. Here an experienced unit midwife is invaluable, as a doctor may not always be readily available. In this series two cases of occult cord prolapse were detected in this way by the sister on duty. The attendant dangers of flexed legs in breech presentation will be discussed in more detail later.

At St. David's Hospital each breech presentation, at the commencement of labour, is put on a quarter-hourly foetal heart chart until the cervix is fully dilated. In the second stage of labour the foetal heart rate is recorded every five minutes or after every pain. This is most important. The second of our foetal deaths, already referred to, could, I think, have been prevented if this principle had been adhered to but, owing to pressure of other deliveries, the duty midwife could not give the case her full attention. The foetal heart was inaudible fifteen minutes after being recorded at 118 beats per minute. Immediate breech extraction failed to obtain a live baby.

Towards the end of the first stage of labour the labour ward staff make the following preparations:

(1) A tray is prepared with syringes drawn up containing:
  (*a*) Atropine sulphate gr. 1/100.
  (*b*) Sodium thiopentone ½ g. in 5 per cent solution.
  (*c*) Ergometrine 0·5 mg.

(2) The anaesthetic trolley is made available in the labour room.

(3) A trolley is prepared as for a forceps delivery.

(4) The patient's stomach is emptied by Ryles' tube or by a stomach tube. (No solid food matter is given to patients in the labour suite.)

(5) When the cervix is deemed to be fully dilated or the breech is visible at the vulva the doctors on duty are informed.

Two doctors must always attend at each breech delivery, one of whom is prepared to give an anaesthetic. Ideally, a paediatrician is also in attendance, but usually the duties of paediatrician and anaesthetist are combined.

The Delivery

(1) The patient is placed in the lithotomy position with the buttocks overlying the edge of the table by 3–6 inches. She is draped in the usual manner and the bladder is emptied by catheterization. She is encouraged to bear down forcibly with each pain.

(2) The atropine is given intravenously.

(3) When the presenting breech commences to distend the perineum, that is, has reached the pelvic floor, the vulval tissues are infiltrated with local anaesthetic and episiotomy is carried out (*vide infra*).

(4) When the buttocks have been delivered by spontaneous effort on the part of the mother or by groin traction by the attendant, anaesthesia is induced rapidly by intravenous injection of thiopentone and the baby thereafter is extracted as quickly as possible consistent with safety to the baby and the mother. The arms are brought down by the method thought most suitable to the situation. If an arm becomes nuchal it is considered to be obstetrical mismanagement. This complication can easily be prevented by pressure of the attendant's forefinger along the foetal humerus as the trunk is being rotated. The head is delivered by the Mauriceau-Smellie-Veit or Burns-Marshall manœuvre (Burns, 1934; Marshall, 1934). If any difficulty is experienced the foetal legs are given to an assistant to hold and forceps are applied to the after-coming head to effect delivery.

If the head tends to remain above the pelvic brim a combination of the Mauriceau-Smellie-Veit manœuvre, using strong pressure of the forefinger in the mouth to flex the head, and supra-pubic pressure is resorted to. Occasionally lateral rotation of the head with the finger in the mouth is necessary to make the head engage easily in the brim. The attendants are not allowed to attempt to apply forceps to a head which is not in the pelvic cavity. Application of forceps to a head above the brim usually results in an extension of the head due to the chin or nose impinging on the sacral promontory and will result in foetal cerebral haemorrhage in most cases. If forceps have to be applied above the brim the case has not been assessed properly in the first instance.

At the St. David's Hospital the house surgeons are instructed in each method of delivering the arms and after-coming head in sequence until they are competent at each method, for we believe with Macafee (1956) that no set method of delivery should be followed. A good obstetrician should be able to resolve any difficulty by a battery of counter moves.

(5) Ergometrine 0·5 mg. is given intravenously when the baby's mouth appears in the cleft of the episiotomy.

(6) The baby is handed over to the care of the paediatricians. Its trachea and larynx are immediately sucked free of mucus and debris.

The outline given above is that of the standard method of breech delivery as employed in the greater number of the cases with which this paper is concerned. From Table VI it will be seen that a number of cases was delivered under pudendal block analgesia. Pudendal block was employed during the first three-year period of the series in selected cases. Subsequently it was decided to employ pudendal block with local perineal and vulval infiltration as the routine method of delivery in the department. Thiopentone was to be withheld and only employed when the delivery proved unexpectedly difficult or when the patient was unco-operative. All patients at St. David's Hospital are still prepared as in the above summary and given atropine intravenously in case thiopentone anaesthesia will be necessary, but the delivery is carried out under pudendal block. The results so far have been most encouraging and a big danger to the mother has, to a large extent, been eliminated (*vide infra*).

The Episiotomy

This must be deep enough to neutralize the curve of the soft tissues of the outlet. The desired depth can be judged by running the forefinger down the posterior wall of the pelvis. The bleeding vessels are either clamped or undersutured. It is stressed, in agreement with Johnson *et al.* (1956) that the greatest obstacle to the delivery of the arms and after-coming head, in the absence of cervix and a contracted bony outlet, comes from the soft tissue resistance of the pelvic floor. It is surprising how easy an apparently difficult extraction of the after-coming head becomes when the episiotomy is deepened.

The only exception to not carrying out a routine episiotomy in every breech delivery is the multigravid patient with a loose or absent perineum or where a small breech presents in a multigravid patient whose perineal tissues appear adequately pliable.

Definition of Terms Used in This Article

(1) *Assisted Breech Delivery*

The outline of the treatment in St. David's Hospital given above is that of the straight-

forward case of breech delivery or what has become known in modern obstetrics as an "assisted breech delivery" (Table I) but it is in fact a modified form of breech extraction. It only differs from "Full Breech Extraction" in that the buttocks are first "presented to the hand" by the mother's efforts before administering the anaesthetic.

(2) *Full Breech Extraction*

By this it is indicated that the mother is deeply anaesthetized before the buttocks have been delivered and the baby is therefore extracted *in toto*, starting off, in most cases, by bringing down the legs.

(3) *Spontaneous Breech Delivery*

Here the baby is delivered entirely by the expulsive efforts of the mother and a guiding influence only on the limbs and after-coming head is exerted by the attendant.

Analysis of St. David's Hospital Figures

There were 218 single breech deliveries in babies ranging from 1 pound 4 ounces upwards. The total stillbirths and neonatal deaths was 51. This total is corrected by excluding 49 cases for the reasons given in Table II.

Table II

	Cases
Accidental haemorrhage	8
Foetal abnormalities incompatible with life	15
Severe toxaemia requiring induction at 30 weeks	1
Eclampsia requiring induction at 30 weeks	3
Intra-uterine death before onset of labour	8
Placenta praevia	3
Hydrops foetalis	2
Premature labour	9
Total	49

The 9 cases of premature labour are analyzed further as shown in Table III.

Of the 169 babies remaining after exclusion of the 49 corrected foetal deaths, 4 were associated with advanced degrees of placenta praevia and delivery was by lower uterine segment Caesarean section. Excluding these 4 babies we are left with 165 babies presenting by the breech. It was out of these 165 cases that we lost 2 infants from asphyxia. They were both in parous patients and have already been referred to. There were no infants lost in the 72 primigravid patients in the series. The smallest baby surviving in the series was 3 pounds 10 ounces. One hundred and thirty-eight babies were delivered vaginally, and in the remaining 27 cases lower uterine segment

Table III

Maturity in Weeks	Cause of Premature Labour	Weight		Result	Remarks
		Pounds	Ounces		
33	Maternal pneumonia	2	2	Died	
33	Premature rupture of membranes	3	5	Stillborn	Trunk born to umbilicus for 1 hour before admission.
30	Unknown	2	7	Died	
28	Unknown	2	4	Died	
28	—	3	14	Died	Post-mortem report: "Prenatal asphyxia due to gross placental insufficiency"
28	Unknown	2	6	Died	
26	Unknown	2	4	Died	
26	Unknown	1	14	Died	
24	Unknown	2	0	Died	

Caesarean was carried out. The Caesarean section rate was therefore 16 per cent of our 165 cases. The indications for Caesarean section are summarized in Table IV.

TABLE IV

Indications for Caesarean Section	Primiparae	Multigravidae
Age	6	–
Obstetric history	2	4
Age + big baby	3	–
Big baby	1	–
Big baby (flexed legs)	1	–
Inco-ordinate uterine action	1	–
Failed trial labour (inco-ordinate uterine action)	4	–
Foetal distress	2	–
Toxaemia	1	–
Contracted pelvis	2	–
Total	23	4

The 4 Caesarean sections on multigravidae and 16 of the Caesarean sections on primigravidae were elective. The most pressing indications for elective operation in all groups were related to the age of the patient in 9 cases (Racker, 1943) and the previous obstetric history in 6 cases. In the advanced age group none of the patients was younger than 36 years. Only 2 patients, of ages 36 and 37 years respectively, in the series escaped operation. The babies in both these cases were estimated as below 7½ pounds.

The outcome of the 138 vaginal deliveries is as shown in Table V.

TABLE V

	Cases	Per cent
Assisted breech delivery	84	60·8
Full breech extraction	25	18·2
Spontaneous breech delivery	29	21
Total	138	100

The form which the anaesthesia took is as shown in Table VI.

Eighteen of the 138 cases delivered vaginally had other complications in addition to that of the breech presenting. These were not considered severe enough to indicate elective Caesarean section.

They are given in Table VII.

TABLE VI

		Per cent
Full inhalation anaesthesia	9	6·5
Thiopentone / Thiopentone + inhalation	70	50·7
Pudendal block	19	13·7
Local analgesia only	16	11·6
Nil	24	17·3
Total	138	100

TABLE VII

Toxaemia	13
Bilateral ovarian cysts	1
Macrocytic anaemia	1
Iron deficiency anaemia	2
Quiescent pulmonary tuberculosis	1

In only one of the toxic cases in Table VII were the complications severe enough to merit breech extraction.

Size of Babies

In the 49 primigravid patients delivered vaginally there were 7 infants of more than 8½ pounds; the biggest baby was 8 pounds 14 ounces. In the 89 parous patients 10 infants were more than 8½ pounds, the biggest baby being 10 pounds 14 ounces.

Birth Injury

One case of fracture of the clavicle occurred in the series.

Results of Breech Delivery in Years 1948–1954

At this stage before proceeding to a more specific analysis of the Bangor results it is considered worth while, for comparative purposes, to present the results of breech delivery at the hospital for the 6 years prior to the period of the present investigation: that is from

January, 1948 till April, 1954. This period is chosen for two reasons:

(1) The records for the hospital, from the year of the inception of the Health Service in 1948, are fuller and more easily obtainable than those prior to this date.
(2) The figures are numerically comparable.

During the period a variation was observed in the method of breech delivery employed. Thiopentone was little used. More particularly, in the early part of the period, the emphasis was on the older teaching which then employed the slower method of breech delivery—in fact, the old "Hands off the Breech" technique. Moreover, the importance of team work and the supervision of house surgeons at delivery was not so emphasized as it was in the period 1954–1958.

During the period 1948 till 1954, 214 breech deliveries took place at St. David's Hospital. The total foetal loss was 31 infants. Applying the same corrections as in the present series the corrected foetal loss in babies above 3 pounds 10 ounces was 11. That is 11 infants in 194 breech deliveries—an incidence of 5·6 per cent.

In the same period, 36 Caesarean sections were carried out—an incidence of 17·5 per cent.

Overall in the 10 years 1948–April, 1958, 359 babies above 3 pounds 10 ounces were delivered at St. David's Hospital with a corrected loss of 13 babies—an incidence of 3·6 per cent. This result is still well within the 3 to 5 per cent loss expectation of Cox (1950) for teaching hospitals.

It is now proposed to examine more specifically the St. David's figures for the period 1954–1958, with the object of stressing certain aspects of breech presentation which appear of particular importance to the writer.

Trial of Labour

Trials of labour were carried out on 10 cases according to Table VIII.

The 4 cases in which a trial of labour ended in Caesarean section all exhibited inco-ordinated uterine action, which was the primary indication for operation (Table IV). This finding, in conjunction with the outcome of the other cases in Table VIII, supports the contention that trial of labour in breech presentation is a feasible and safe procedure. The large size of the babies in which labour failed should be noted particularly.

Length of Labour

The average length of the first stage of labour in primigravidae was 11·3 hours and in multigravidae 8·6 hours. The length of the second stage was in primigravidae 39·2 minutes and in multigravidae 20·3 minutes. The range of

TABLE VIII

Indications for Trial	Outcome	Primigravidae Weights of Babies		Multigravidae Weights of Babies	
		Pounds	Ounces	Pounds	Ounces
Big baby and capacious pelvis	Caesarean section (4 cases)	9	2		
		8	6		
		9	3		
		8	4		
(7 cases)	Extraction (1 case)			8	0
	Assisted delivery (2 cases)			7	8
				8	14
Borderline pelvis; average baby (1 case) ..	Extraction	6	9		
Vaginal examination impossible (1 case) ..	Spontaneous			6	9
Bilateral ovarian cysts .. .. .. (Pushed up during labour)	Assisted	7	3		

labours was from 2 to 44 hours in primigravidae and from 1 to 37 hours in multigravidae. Only 10·4 per cent of primigravidae and 11 per cent of multigravidae had labours lasting over 20 hours. The implication of these facts will be discussed in more detail later.

Length of Gestation

Out of the 218 cases in the uncorrected series, labour started spontaneously about the 40th week of gestation in 139 cases. In the 79 cases which went past the expected date of confinement the onset of labour took place according to Table IX.

TABLE IX

44 cases went 1 week or more past expected date of confinement.	
24 cases went 2 weeks or more past expected date of confinement.	
8 cases went 3 weeks or more past expected date of confinement.	
3 cases went 4 weeks or more past expected date of confinement.	

Therefore only 11 cases (5·5 per cent) went past the 42nd week of their gestation period. In fact, postmaturity in breech presentation is a rare occurrence.

Two of the patients whose pregnancy went as far as 44 weeks were induced surgically, one by membrane sweep and the other by artificial rupture of the forewaters. (These were the only surgical inductions carried out in the series.) The third case, on the assumption that the patient was probably a month out in her dates, was allowed to come into spontaneous labour.

One baby of 43 weeks maturity in a primigravida of 38 years was delivered by lower uterine segment Caesarean section because of the onset of foetal distress after labour had been progressing for 14 hours. This patient in the normal course of events would probably have had an elective Caesarean section at term but she defaulted from the prenatal clinic and did not present herself in hospital until labour was well advanced.

POSITION OF THE FOETAL LEGS AS A FACTOR INFLUENCING FOETAL SAFETY

In the uncorrected series of 218 breech presenting babies the foetal legs were extended in 141 cases and flexed in 42 cases. In 6 cases one leg was flexed and the other extended, and in 29 cases the position of the legs was not recorded. The legs were extended therefore in 74 per cent of the recorded total. In babies over 5½ pounds the legs were extended in 77·8 per cent of primigravidae and 77·7 per cent of multiparae, an interesting comparison and one which is perhaps not unexpected in view of the suggested cause of breech presentation (*vide infra*).

In the 42 cases in which the legs were flexed delivery was expedited in 21 cases (50 per cent). This took the form of full extraction in 20 cases. The remaining case was treated by lower uterine segment Caesarean section. The indications for interference are summarized in Table X.

TABLE X

	Cases
Prolapse and presentation of the cord	8
Delay in the 2nd stage (5 cases associated with foetal abnormalities)	8
Foetal distress (1 treated by Caesarean section)	4
Prolonged 1st stage ending in maternal distress	1
Total	21

Flexed legs are therefore regarded by the writer as a dangerous complication of breech presentation and one that requires:

(1) Increased supervision of the woman in labour.

(2) Skill and judgment to anticipate the time and mode of delivery.

(3) Experienced obstetrical skill at the delivery.

If these precautions are difficult to realize, then due regard should be paid to the necessity of carrying out Caesarean section as a prophylactic measure. Certainly in cases where other factors are indicating Caesarean section the presence of flexed legs should weigh heavily.

FIG. 1

Photograph of uterus after completion of Caesarean section. Uterus previously reported with hysterograph as uterus unicornis (Hay, 1958). Note vestigial bud of left uterine horn.

The practice of pulling down a leg in order to encourage better pains in cases of flexed breech is to be condemned because:

(1) It rarely achieves this object.

(2) It encourages the obstetrician to attempt a breech extraction later on through an undilated cervix.

(3) It endangers the life of the mother if Caesarean section is ultimately resorted to, since an infected leg must be pulled up through the abdominal wound.

Pitocin drip infusion intravenously or Caesarean section are safer alternatives.

In this series it was also found that cases in which one leg was extended and one flexed behaved very much as those in which both legs were flexed. Of the 6 cases in which this occurred 3 were delivered by elective Caesarean section for other indications, but the remaining 3 cases had to be delivered by breech extraction.

Prolapse and Presentation of the Umbilical Cord

In the 42 cases of flexed legs the cord prolapsed or presented 8 times, an incidence of 20 per cent. Six of these cases appear in the corrected series of 165 cases. Breech extraction was carried out in each case and all babies survived. In 3 of the cases the prolapse occurred at or near full dilation of the cervix. In a 4th case the cord was palpated looped around the foetal leg at half dilation of the cervix. This was in a parous patient with a history of quick labours. The theatre was prepared for Caesarean section. There was no irregularity of the foetal heart. Extraction was eventually carried out when the cervix was more safely dilated. In the remaining 2 cases the cord was palpated between the foetal legs through the membranes. Extraction was carried out in each case as the cervix was safely dilatable. Five of the cases of prolapsed cord or cord presentation were associated with multigravidae. The only primigravid patient in whom the cord prolapsed proved on hysterography after delivery to have a unicornate uterus (Hay, 1958). The cord prolapsed in this case at full dilation of the cervix.

This patient in her second pregnancy also went to term with a flexed breech presenting. In view of the past history vaginal examination was carried out under trilene analgesia in the theatre. The cervix was soft and easily dilatable to admit two fingers. As feared, the cord could be palpated inside the bag of forewaters amongst the foetal legs. Lower uterine segment Caesarean section was therefore carried out. A small vestigial remnant of the left horn of the uterus was found attached low down to the wall of the pregnant cavity. There was no appreciable connexion between this vestigial bud and the cavity. The uterus was photographed (Fig. 1).

As the patient was operated upon after completion of the present series the details of her second pregnancy do not appear in the present statistics.

In no case in this series of breech presentations was prolapse of the cord associated with an extended breech.

Retained Placenta

Manual removal of the placenta was carried out 26 times in the 191 cases which were delivered vaginally in the series as a whole—an incidence of 13 per cent. Sixteen of these were in multigravidae and 10 in primigravidae. In a previous paper (Hay, 1958) it was pointed out:

(1) Uterine abnormalities are probably the primary cause of breech presentation.

(2) The incidence of retained placenta in association with known cases of uterine abnormality is 7 to 12 per cent.

It would appear therefore that the increased incidence of retained placenta in association with breech presentation is in keeping with the fact that breech presentation itself is related to abnormalities of the uterus.

The Cause of Breech Presentation

Exploration of the birth canal was carried out under general anaesthesia after completion of the second stage of labour in 37 cases. Pregnancy had gone to full term in each instance. In some cases exploration was necessary because of a retained placenta but, for the most part, it was done as a routine procedure in furtherance of a previous investigation by the writer into the

association of minor degrees of uterine abnormality in relation to pregnancy (Hay, 1958). In this paper it was demonstrated that the bilateral pocketing found at the fundus of the uterus in association with breech presentation and other complications of pregnancy was a sign of uterine abnormality. In 36 of the 37 cases explored in this series signs of uterine abnormality were found as indicated by the presence of bilateral pocketing at the uterine cornua.

Ten of the cases were associated with flexed legs, and there were 2 cases where one leg was extended and one flexed. In fact, breech presentation appeared to be associated with abnormalities of the uterus irrespective of the position of the foetal legs.

In the previous paper by the writer already referred to, it was shown that a foetus with extended legs when associated with a uterine abnormality tended to present by the breech. This is because the foetus, whilst undergoing spontaneous version movements *in utero* (Vartan, 1945), eventually reaches the optimum size in relation to the uterine cavity where it is unable to make its final spontaneous cephalic version because its head becomes impinged in the sac of the uterine abnormality. This occurs around the 34th week of pregnancy. The foetus with its head in the sac is at a mechanical disadvantage because of its extended attitude and rigidity. If the legs are flexed it can still complete spontaneous cephalic version by flexing its trunk.

But there is no reason why, if the legs are flexed, the foetus should not also find itself occasionally in the unhappy position of not being able to get its head out of the sac. This eventuality implies, in theory, a bigger sac, or, in fact, a greater degree of uterine abnormality. This is borne out clinically and some of the most advanced types of uterine abnormality encountered by the writer were associated with flexed legs: Figure 1 and Hay (1958, Table XI). As compared with the flexed breech the increased difficulty of the extended breech in freeing its head from the sac is reflected in the increased incidence of extended breech (78 per cent) as compared with the flexed breech (22 per cent).

On the other hand, there is no reason why, by the laws of chance, one should not occasionally find a breech in a normal uterus. This occurs more often in association with the flexed breech than with an extended one. The one normal uterus found at exploration in the 37 cases investigated after delivery in this series was associated with a flexed breech.

There are several incidental factors which help to consolidate further this theory of the origin of breech presentation:

(1) In babies over 5½ pounds the incidence of flexed and extended legs in both primigravidae and multigravidae is exactly the same.

(2) The incidence of retained placenta after breech delivery and in cases of known uterine abnormality are comparable.

(3) The incidence of breech presentation remains at 3 per cent in spite of the practice of "external cephalic version" (*vide infra*).

(4) The incidence of sub-involution after breech presentation and with cases of known uterine abnormality is the same (*vide infra*).

Involution

Forty-seven of the 137 cases in which the size of the uterus in the puerperium was recorded showed evidence of delayed involution—an incidence of 35 per cent. Thirty of the recorded cases were in multigravidae and 17 in primigravidae. This high incidence of sub-involution is comparable to the previously reported incidence of 38 per cent in cases of uterine abnormality generally (Hay, 1958).

Discussion

Breech Extraction

It must be emphasized at the outset that the standard method of breech delivery for the St. David's Hospital, although presented in this paper as "Assisted Breech Delivery", is, in fact, technically a breech extraction. It differs from Full Breech Extraction only to the extent that either the mother partially delivers the breech by her own efforts or the breech can be easily delivered by groin traction. The ability to initiate the delivery of the breech in either instance is, in principle, an act which guarantees the safety of the baby, for it indicates two facts:

(1) The cervix is fully dilated if the breech is an extended one and probably widely enough dilated to continue the delivery with safety if the breech is flexed.
(2) There is unlikely to be cephalo-pelvic disproportion at the brim of the pelvis.

If the outlet has already been judged to be satisfactory it is therefore safe to continue with the delivery in the form of extraction with all possible expedition. This should be no more difficult than a technical exercise. The extraction aims at cutting out completely the danger to the foetus of asphyxia but it must not be so forceful as to subject the baby to the other danger always associated with breech delivery—that of trauma to the vital organs and after-coming head, particularly the latter.

Technically, as far as the foetus is concerned and in proper hands, and if the obstetrician knows already that the conditions are satisfied which the act of presenting the buttocks to the hand signifies, there is no reason why Full Breech Extraction should not be safely practised as a routine method of breech delivery. Johnson *et al.* (1956) do in fact adopt this practice with a corrected foetal loss for full-term infants of 0·9 per cent. Dieckmann and Harrod (1955) practise full breech extraction in 43 per cent of their cases with a similar foetal loss. They quote Goethals as having the same foetal loss as themselves (0·9 per cent). Goethals also carries out full breech extraction to a large extent, although his main emphasis like Dieckmann and Harrod is on the modified form of extraction as expressed in "manual aid" (Table I).

There is no doubt that the chief danger to the foetus when bony contraction of the pelvis has been excluded lies in the soft tissue resistance of an undilated cervix or in the perineal and levator muscles. As regards the former, extraction should not be embarked upon until the cervix is fully dilated. The resistance of the perineal and levator tissues can be easily overcome by a deep episiotomy.

A review of the literature satisfies the writer that the best results in breech delivery are achieved by breech extraction or its modified forms, as can be seen from Table I. The Liverpool results were greatly improved when the "Hands off the Breech" technique was replaced by the modified breech extraction method described by Marshall (1934) and Cox (1950) and referred to by Cox as "Assisted Breech Delivery".

Macafee (1956) lays great stress on the dangers of breech extraction and quotes a figure of 20 per cent foetal mortality in reference to published hospital reports. The writer agrees but one should be careful in the interpretation of these figures in the light of our American colleagues' results (Table I). Macafee's figures indicate surely, for the most part, that the cases in which extraction was practised were not properly assessed in the first instance, before the extraction was attempted. Undoubtedly there is always a grave danger to the foetus associated with a difficult breech extraction, but a wise obstetrician should not leave himself with this eventuality. The alternative to a possible difficult breech extraction is Caesarean section. Macafee's figure should not be used therefore to decry the safety of breech extraction in the properly assessed case, but rather to support the need for avoiding a difficult breech delivery.

The writer is not advocating routine breech extraction as a method of delivery, since the Bangor figures prove that that is not necessary. It is realized that full breech extraction in most cases demands full surgical anaesthesia and this employed as a routine must inevitably result in maternal loss or foetal injury. Our American colleagues do not quote any figures for maternal deaths but Dieckmann and Harrod (1955) give the following:

> In 1,061 breech deliveries there were 2 ruptured uteri.
>
> Of their live babies 2·2 per cent had traumatic injuries.
>
> In 78 stillbirths 15 per cent had intracranial damage.

One cannot safely carry out a full breech extraction in an extended breech without full ether anaesthesia sufficient to relax the muscular spasm of the lower segment (Johnson *et al.*, 1956) to enable the legs to be brought down after the breech has been disimpacted. If the legs are flexed, extraction only requires a minimum of anaesthesia and the delivery is correspondingly easier—provided the cervix is fully dilated.

By employing the "buttocks in the hand" technique one eliminates dangerous anaesthesia. This is the aim of modern British obstetrics (Jeffcoate, 1953; Parker, 1954; Scott and Gadd, 1957). With the increased use of pudendal block as an alternative to thiopentone anaesthesia in the St. David's Hospital a further step is being taken in this direction.

In principle, the indications for full breech extraction at St. David's are the same as for forceps delivery, namely:

(1) Foetal or maternal distress.

(2) Delay in the second stage of labour.

(3) To minimize the dangers to the mother of bearing down efforts in dangerous conditions associated with pregnancy.

Also the same conditions, as for forceps delivery, should be satisfied before embarking on breech extraction, namely:

(1) The baby must be safely deliverable. This implies careful pre-natal assessment of the pelvic-foetal relationship.

(2) The cervix must be fully dilated.

(3) The breech must be showing at the vulva.

The only alternative to No. 3, that is for the delivery of a breech from a higher station than the outlet, is that the baby is small compared with the pelvic capacity and the foetus obviously remains high because of either poor second stage pains or the resistance of the soft tissues of the outlet. However, it must be stressed that this eventuality is rare, and an obstetrician faced with the possibility of a breech extraction from a higher station than the outlet would be wise to reassess the whole situation. If there is any doubt in his mind even at this late stage about the pelvic-foetal relationship, Caesarean section is still the safer method of delivery. The way of no return has been embarked upon once the legs have been delivered.

Apropos of the above, the obstetrician must exercise extreme caution in those cases in which a trial of labour has arrived at the stage where the breech fails to advance in the second stage of labour. It should be remembered that the labour in these cases has already started off on a questionable basis as regards the pelvic-foetal relationship (*vide infra*).

Trial Labour

This has now come to be accepted as a safe procedure where there is some doubt about the pelvic-foetal relationship. Marshall (1934), Cox (1950), Dieckmann and Harrod (1955), Law (1955) and Macafee (1956) in the recent literature are all in favour. Only Calkins (1955) is in disagreement. Kaltreider (1957) thinks there are safer methods dependent on X-ray pelvimetry and cephalometry.

In principle, labour is allowed to commence spontaneously and this usually occurs before the 42nd week of pregnancy (see text). Nature is relied upon to demonstrate the inadequacies of the obstetrician by encouraging the uterus to exhibit inco-ordinate uterine action if there is pelvic-foetal disproportion present (Table IV). This kind of approach to an obstetrical problem is not very scientific but it appears to work satisfactorily in the large majority of cases. It has also the merit of being safe, but only if one recognizes that nature cannot always be relied upon. Occasionally she lets the obstetrician down by the uterus exhibiting co-ordinate contractions in the presence of pelvic-foetal disproportion. Under the action of good pains the breech either: (1) descends to the pelvic outlet in the second stage only to fail to advance further, or (2) fails to descend into the pelvis.

It is in the first type of case that the obstetrician is most likely to make a mistake. In the experience of the writer, unless the breech is showing with the pains or can be pushed down to show at the vulva by trans-abdominal pressure on the foetus it is probably safer, even at this late stage, to resort to Caesarean section rather than to embark on a difficult breech extraction. Particularly is this so if there is any doubt about the pelvic outlet. It seems hardly necessary to point out that if the breech is at a higher level than "visibility", or if it fails to descend under the action of co-ordinate uterine contractions, then Caesarean section is the only safe procedure.

In the absence of pelvic-foetal disproportion a trial of labour proceeds to present "the buttocks in the hand".

It should be stressed that trial of labour with the breech presenting only tests the pelvic-foetal relationship as it exists at the brim and in the

cavity of the pelvis. Any contraction at the outlet can be very much more lethal to the infant than if the vertex presents.

Failure to realize this fact adequately resulted in the only stillbirth from cerebral haemorrhage that the writer has had personally in nine years of major hospital obstetrical experience. In this case there was a moderate degree of pelvic outlet contraction as judged by the sub-pubic-coccygeal diameter. The baby which prenatally was estimated as being less than 7 pounds was, in fact, nearly 8 pounds in weight and the maximum circumference of the foetal head measured 15 inches.

Inco-ordinate Uterine Action

The writer agrees with others, notably Cox (1950, 1957), Daley and Michael (1953), Dieckmann and Harrod (1955), and Macafee (1956) that inco-ordinate uterine action can be most dangerous in breech presentations. Its persistence should be a primary indication for Caesarean section. Since it has already been pointed out that the majority of cases of pelvic-foetal disproportion in trial labour exhibit inco-ordinate uterine action (Table IV) obstetricians should be quick to recognize the complication. In the text of the paper it is shown again (cf. Calkins, 1955; Macafee, 1956; Cox, 1957) that the average length of normal labour in both primigravid and multigravid patients, when the breech presents, is around 11 hours. Any extension of labour beyond this limit should be regarded with concern. Dieckmann and Harrod (1955) state that 18 hours should be the outside acceptance of the length of labour.

In this series the average length of the second stage of labour in primigravidae was found to be 39·2 minutes, not the 1 to 1½ hours as stated by Cox (1950). The explanation of this difference is simple—episiotomy carried out at an earlier stage. In a normally proceeding labour the length of the second stage can be cut down considerably by early deep episiotomy, since most of the delay of the second stage is taken up by making the uterus and patient overcome the soft tissue resistance of the levator and perineal muscles. Since the obstetrician is going to perform an episiotomy in any case it seems unnecessary and unwise to delay doing so until the act of parturition has extended to the wide distension of the soft tissues of the outlet. This is contradictory to the teaching of Cox (1950, 1955, 1957).

Prolapse of the Umbilical Cord

The danger of prolapse of the cord in association with the flexed breech has been stressed by most writers in the past. The whole critical situation that the foetus faces when its legs are flexed was pointed out originally by Marshall (1934).

The writer in this paper has only attempted to bring into greater prominence the modern implication of the old concept, since little notice still appears to be attached to the position of the foetal legs when deciding the method of delivery. As expressed in the text of this paper the position of the foetal legs is most important and flexed legs should be regarded as a potentially lethal complication.

The tendency in modern reporting of breech successes is to correct for and exclude foetal deaths due to prolapse of the cord. Cox (1950), for example, eliminates one foetal death due to this complication. He is not impressed with the supposed dangers to the foetus of flexed legs compared with extended legs, but he has eliminated 23 cases of prolapsed cord from his corrected series of 1,004 cases, and these most likely were associated with flexed legs. The inclusion of Cox's one foetal death due to cord prolapse would not have affected his final result materially. Dieckmann and Harrod (1955), on the other hand, exclude 6 babies lost out of 17 cases in which the cord prolapsed. They say they have certain misgivings about it. Calkins (1955) states "Prolapse of the cord is, in our experience, not only more frequent with breech presentation but also more lethal". Daley and Michael (1953) feel that prolapsed cord is more a complication of breech presentation than uterine inertia.

Table I illustrates (as far as can be ascertained from the writings) the extent to which various writers have corrected for prolapse of the cord. Cox (1950) states that his correction was made because prolapse of the cord is just as common in breech as in vertex

presenting foetuses. This at first analysis would appear to be true, but it is far from being so if the complication in relation to flexed legs is analyzed compared with the presenting vertex. Prolapse of the cord occurred in 20 per cent of cases of flexed legs in the present series (see text).

Since cord prolapse, in the experience of the writer, is so intimately associated with the position of the foetal legs it should be accepted as one of the hazards of breech delivery, not excluded as being unavoidable. Its possibility should be, and can be, anticipated, in most cases, by searching prophylactically for the cord *before* the membranes rupture. Because of the inherent danger of cord prolapse, coupled with the increased interference rate associated with the flexed breech (Table X) the writer urges that resort to Caesarean section should be an accepted obstetric practice in doubtful cases associated with flexed legs. The doubt should extend to:

(1) The pelvic-foetal relationship.
(2) The standard of efficiency of the labour ward personnel.
(3) The obstetric experience of the delivering attendants.

Version

There appears to be considerable confusion in the literature as to the dangers attributable to "external cephalic version" since writers omit to state whether the figures they quote are for version under anaesthesia or for version without anaesthesia.

In Table XI are the reported results for the two methods where the *modus operandi* has been definitely stated.

It is obviously safer nowadays, therefore, with a foetal loss of around 1 per cent for breech delivery, for the baby to be delivered either vaginally as a breech or by Caesarean section in the selected cases than to have "external cephalic version" performed upon it.

The St. David's loss for "external cephalic version" is nil, since in no case was version practised according to the accepted interpretation of the term. The incidence of breech delivery at St. David's Hospital is 2·9 per cent. This is in keeping with figures published by other writers, e.g., Calkins (1955) 3·8 per cent, Kaltreider (1957) 3·34 per cent, Daley and Michael (1953) 3·7 per cent, Vartan (1945) 2·2 per cent. Some of these writers are known to practise "external cephalic version". The others presumably do so. In fact, the incidence of breech delivery is the same irrespective of whether or not external cephalic version is practised. All obstetricians are aware of the cephalically versed foetus which presents again as a breech on another occasion, or of the foetus which, presenting as a breech and persistently defying all attempts at version, spontaneously undergoes cephalic version just before term (Vartan, 1945). In fact, all the obstetrician would appear to do by carrying out an apparently successful external cephalic version

TABLE XI

	Under Anaesthesia		Without Anaesthesia	
	Percentage Foetal Loss	Corrected to Include Infants Lost Afterwards in Labour—Percentage	Quoted by Macafee and McClure (1937)	Percentage Foetal Loss
Peel and Clayton (1948) ..	1·7	3·8	Macafee and McClure ..	0·74
Freeth and MacVine (1951)	1·4	2·3	Gibberd	2
Newton (1949)	2·6	7·1	Allan	Nil
Wrigley (1934)	—	13	Sloan Hospital for Women	2·2
			White	5

is to anticipate an act which nature would have accomplished with more safety to the baby at a later date. It would seem, therefore, that the practice of external cephalic version is an unnecessarily dangerous adjunct to modern prenatal care.

The fact that 3 per cent of babies will always present by the breech irrespective of attempts of obstetricians to make them present otherwise supports the view of the writer that the cause of breech presentation is intrinsic in the uterus itself.

Caesarean Section

There is no doubt that the low foetal death rate in modern breech statistics is due to the increasing use of lower segment Caesarean section as a method of delivery. The St. David's Hospital figure of 16 per cent is high but is in keeping with modern trends (Table I).

Is Caesarean section a justifiable alternative to "external cephalic version" in those cases where the pelvic-foetal relationship is in doubt? For the avoidance of a possible difficult breech extraction would now appear to be the only remaining justifiable excuse for attempting external cephalic version. The answer to this question will obviously depend on the relative safety of the two methods of approach to this situation. The dangers of "external cephalic version" we have already presented.

Cox (1950) quotes a figure of 2·5 per cent foetal loss for elective section in 125 cases of breech presentation at Liverpool. This is, however, in keeping with the expected foetal loss for elective section generally over the period to which Cox's paper refers. This was reported in 1949 for teaching hospitals as 3·3 per cent (Marshall and Cox, 1949). Dieckmann and Harrod (1955) cite 1·1 per cent as their corrected foetal loss for elective section on 123 cases of breech presentation and 4·5 per cent loss for elective operations for the hospital as a whole (the period covered is not reported).

In the last 20 years at St. David's Hospital 109 lower segment Caesarean section operations were performed on breech presenting babies for various indications with the loss of one baby due to "atelectasis". This one loss is not outside the realms of chance. In the last 11 years at St. David's 650 elective lower segment operations were carried out for various reasons but including some of the breech cases. The corrected foetal loss was 4 infants (0·6 per cent). In the 1,098 lower segment operations carried out at the hospital for indications of all types in the same 11-year period the corrected foetal loss was the same 4 infants (0·36 per cent). Correction was made for babies lost due to placenta praevia, prematurity, foetal abnormalities, accidental haemorrhage, toxaemia, rhesus incompatibility and foetal distress before operation (3 cases).

The writer finds it difficult to believe that Caesarean section with a baby presenting by the breech should carry a higher foetal mortality than the equivalent operation on the vertex-presenting baby. He feels that 0·5 per cent foetal loss should be a fair expectation for the lower segment operation on breech presentation with due regard to modern anaesthetic techniques and improvements in ancillary aids. Amongst the latter he would list high the presence at every delivery of a paediatrician skilled in the methods of resuscitation. These include at St. David's intra-gastric oxygen and Gibberd's resuscitation apparatus. The stomach of all Caesarean delivered babies is aspirated and washed out as a routine. The value, too, of an expertly run premature and resuscitation unit for the reception of the baby after delivery is immense. St. David's Hospital is singularly fortunate in this respect.

From the foetal point of view, therefore, the results for Caesarean section compare favourably with those expected from "external cephalic version" in borderline cases.

What of the maternal risk for lower uterine segment Caesarean section? The corrected maternal death rate for teaching hospitals generally up to 1949 for elective operation was 0·13 per cent and the uncorrected rate for all cases of lower segment operation 0·99 per cent (non-teaching hospitals—0·97 per cent and 1·32 per cent respectively) (Marshall and Cox, 1949; Purdie, 1949).

The 1,098 lower segment operations at St. David's already referred to were performed with the overall loss of 7 mothers (0·63 per cent). Correcting for "cases of favourable omen"

(Marshall and Cox, 1949) but still including those cases operated upon after labour had commenced, the maternal death rate was 0·28 per cent. Our corrected maternal loss for the 650 elective operations was 2 mothers (one from pulmonary embolism and one from paralytic ileus). Both operations were on elderly patients. The expected maternal loss is, as Cox (1950) states, "low indeed" but it is still higher than the expected maternal death rate for normal vaginal delivery.

The high maternal death rate due to the operation as compared with the safety of vaginal delivery should discourage the practice of delivering all breech presenting babies by Caesarean section; a practice which, as Cox (1955) states, would take a lot of the satisfaction out of obstetrics. Nevertheless, the relative safety of the operation for the foetus adds weight to the dictum of this paper—"When the outcome for the foetus is in doubt it is safer to carry out Caesarean section".

The Parous Breech

The previously reported increased danger to the foetus presenting as a breech in the parous woman as compared with breech presentation in the primigravida (Cox, 1950; Redman, 1950; Cutts and Abbas, 1951; Daley and Michael, 1953) is adequately expressed in this paper. The writer feels that more care and attention, particularly in the second stage of labour, should be given to the multigravida than to her primigravid sister.

Summary

One hundred and sixty-five cases of primary breech presentation in babies weighing 3 pounds 10 ounces and over are presented with a foetal loss of 1·2 per cent.

The Caesarean section rate is 16 per cent.

Seventy-six per cent of the cases were delivered by the resident staff at the hospital.

Emphasis is placed on careful prenatal assessment of cases, team work, diligent observation of cases in labour, detailed preparation for delivery and experienced obstetrical supervision of the delivering attendants.

The routine method of delivery favours modified breech extraction.

Caesarean section in doubtful cases is encouraged but equally there is a place for trial of labour. The danger of outlet contraction in cases of trial labour is stressed.

The dangers of inco-ordinate uterine action are re-emphasized.

A plea is made for inclusion of cases of prolapsed cord in breech statistics, since it is shown that the complication is intimately associated with flexed legs. The flexed breech is shown to be a potentially dangerous presentation and Caesarean section as a method of delivery is advocated in otherwise doubtful cases where the legs are flexed.

The practice of external cephalic version as an adjunct to prenatal care should be abolished.

Further evidence is presented that primary breech presentation is due to uterine abnormalities.

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URINARY DEVIATION IN GYNAECOLOGICAL SURGERY

BY

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URINARY deviation in gynaecological surgery may be fortuitous or planned. Fortuitous deviation may occur and be recognized at operation: for example, the bladder may be injured during the anterior dissection at hysterectomy, or the ureter may be divided or resected in the region of the uterine vessels, between the anterior vaginal wall and the base of the bladder, or higher up in the vicinity of the infundibulopelvic ligament. At times, fortuitous deviation is revealed only subsequent to operation by the development of a uretero-vaginal, vesico-vaginal, utero-vesical, or vesico-colic fistula: it may be spontaneous and follow malignant infiltration or post-irradiation necrosis. Planned deviation may be brought about by the operations of ureterostomy, pyelostomy or nephrostomy, uretero-colic transplantation, and uretero-ileostomy (ileal bladder): wet colostomy is mentioned only to be condemned while cystostomy is seldom or never required for deviation of the urine in gynaecological surgery.

The case reports presented in this paper have been collected over a period of 10 years: some of the patients were referred from other centres.

FORTUITOUS DEVIATION OF URINE

(*i*) DEVIATION NOTED AT OPERATION

Little need be said about bladder injuries which occur and are noted during a gynaecological operation. A single layer continuous No. 1 chromic catgut suture is usually adequate to effect the bladder closure and an indwelling urethral whistle-tip Foley-catheter (5 ml.) should be kept in position for 7 days: a free omental graft, if available, may be used to reinforce the suture line in the bladder and care should be taken to ensure that the suture does not occlude the ureters.

The divided or resected ureter is a more difficult problem. When the ureter is divided in the region of the uterine vessels, the commonest site of injury in gynaecological operations, it should be re-implanted into the bladder by a mucosa-to-mucosa single layer of 4/0 arterial silk interrupted sutures with a Coffey tunnel 1·5 cm. long in the bladder musculature (*vide infra*). This technique is preferable to simpler methods of implantation (Te Linde, 1946) which are liable to be followed by reflux of urine, pyelonephritis, and subsequent nephrectomy. When the ureteric division is more proximal or where a length of ureter has been inadvertently resected, re-implantation into the bladder is not possible or advisable (it must never be under tension): three possible alternatives are available.

The ideal management consists of isolation of an adequate length of terminal ileum, restoration of continuity of the small bowel by an end-to-end anastomosis, intraperitoneal anastomosis of the distal end of the isolated length of ileum to the fundus of the bladder by a 2-layer continuous catgut suture, closure of the proximal end of the isolated ileal segment by a 2-layer continuous catgut suture, and uretero-ileostomy by a mucosa-to-mucosa anastomosis with a Coffey tunnel (*vide infra*). This procedure, however, is time-consuming and, following a difficult or prolonged gynaecological operation, should be carried out only when the general condition of the patient is satisfactory: its virtue is that urine reflux and subsequent pyelonephritis are avoided.

A less satisfactory alternative, provided the two cut ends of the ureter can be mobilized without devascularization (Daniel and Shackman, 1952) and tension is absent when the ends are approximated, is a direct ureteric anastomosis by interrupted 2/0 chromic catgut sutures. The cut ends must be resected obliquely to minimize the risk of subsequent ureteric stenosis and a size 2 polythene tube may be used to splint the anastomosis: such a tube will be spontaneously extruded by ureteric peristalsis unless it is brought through the uretero-vesical orifice, across the bladder, and out through the urethra before secure fixation to the medial aspect of the thigh by waterproof adhesive strapping. An incision into the bladder may be required for this manœuvre.

Case 1

I.R., aged 41, underwent total hysterectomy for menorrhagia and dysmenorrhoea in March, 1958. The left ureter was inadvertently divided at the level of the infundibulo-pelvic ligament and was immediately reconstituted by three interrupted atraumatic catgut sutures over a length of polythene tubing which was passed down into the bladder and out through the urethra. A rigor occurred 12 days later and was accompanied by spontaneous extrusion of the polythene tubing and a leak of urine thought to arise from a uretero-vaginal fistula. It was felt, at first, that further surgery was indicated: the urine leak, however, did not recur and excretion urograms showed a functioning left kidney with only a moderate degree of hydronephrosis (Fig. 1). A waiting policy was therefore adopted and proved to be justified for the incontinence did not recur and the patient was discharged home 26 days after the hysterectomy. Excretion urography repeated 2 months later showed good renal function on both sides with slight ureteric dilatation on the left side but with no significant calyectasis (Fig. 2).

Ureteric bouginage may be required if further excretion urograms show any hint of ureteric stenosis and obstruction: such X-rays should be carried out at 3-monthly intervals for at least a year.

The least satisfactory procedure for dealing with a proximal division of the ureter is cutaneous ureterostomy: this is preferable to ligation unless it is reasonably certain that the ultimate prognosis with regard to the gynaecological lesion is poor and it is known that the function of the contra-lateral kidney is adequate. The virtue of a cutaneous ureterostomy lies in the fact that subsequent re-implantation into the bladder through an isolated ileal segment may be carried out in three or four weeks. The proximal portion of the cut ureter should be mobilized without separation from its connective tissue sheath and at least 2 cm. should be allowed to extrude through the parietes. The ureterostomy should be brought out in the flank: retraction is less likely to occur and the subsequent uretero-ileo-vesiculoplasty can easily bridge the long gap. A size 2 polythene tube should be tied into the extruded tip of the ureter for convenient conduction of the urine into a closed drainage bottle or, alternatively, a plastic ileostomy bag can be used for the urine collection: open drainage carries a significant risk of ascending infection and is to be avoided.

(*ii*) Deviation Noted Subsequent to Operation

Uretero-vaginal Fistula

Uretero-vaginal fistula may follow hysterectomy or removal of impacted, adherent, or infiltrative pelvic tumours: the gynaecologist who undertakes the most difficult pelvic operations is likely to have a higher incidence of this complication than is the surgeon who limits his activities to the simpler procedures. When recurrent malignant disease after radiotherapy is treated by a Wertheim operation with extensive mobilization of the ureters, there is an increased risk of sloughing and fistula formation: post-irradiation obliterative endarteritis of the small ureteric blood vessels devascularizes such ureters. The complication does not necessarily reflect the surgical prowess of the operator. Nevertheless, it is recognized that imperfections of technique account for some cases of uretero-vaginal fistula: a misplaced or slipped clamp on a uterine artery followed by a brisk haemorrhage and blind clamping are well-known dangers. Rarely, the complication follows an apparently straightforward operation.

Case 2

R.P., aged 48 years, suffered from menorrhagia for one year and underwent an operation for removal of a bulky uterus and polycystic ovaries. Total hysterectomy and bilateral salpingo-oöphorectomy was carried out

without any untoward incident but on the 5th post-operative day there was a sudden vaginal bleed which was followed some days later by a leak of urine. Methylene blue instilled into the bladder through a urethral catheter was not observed on a swab in the vaginal vault and it was concluded that a uretero-vaginal fistula had developed. Excretion urograms (Fig. 3) showed a normal right kidney but gross hydronephrosis on the left side. Cystoscopy showed no bladder abnormality. Laparotomy was carried out. The previous abdominal scar was excised and the peritoneum was stripped back to give an extraperitoneal exposure of a dilated left ureter which was seen to have been transected just proximal to the bladder at the point of ligation and division of the left uterine artery: in fact the divided and ligated artery was clearly seen. The ureter was mobilized, its end trimmed obliquely and re-implanted back into the bladder by a mucosa-to-mucosa single layer of 4/0 arterial silk interrupted sutures and with a Coffey tunnel 1·5 cm. long in the bladder musculature. The bladder was drained by an indwelling urethral Foley catheter for 8 days and the patient was discharged to convalescence on the 19th day. She has remained dry ever since the re-implantation. Excretion urograms taken 14 days after the operation still showed a considerable degree of hydronephrosis but excretion urograms taken three months later, show complete restitution (Fig. 4).

Post-operative vaginal bleeding in such circumstances not uncommonly heralds a uretero-vaginal urinary fistula. Uretero-neo-cystostomy is a preferable alternative to nephrectomy provided the complication is treated within two or three weeks and gross hydronephrosis or severe urinary infection has not developed.

Vesico-vaginal Fistula

Vesico-vaginal fistula may follow hysterectomy for carcinoma of the cervix particularly when the disease has spread forwards.

Case 3

E.W., aged 49 years, was treated by radiotherapy 2 years before she underwent a total hysterectomy and bilateral salpingo-oöphorectomy for recurrent malignant disease of the cervix. There was difficulty in stripping the bladder and the subsequent histology showed deep invasion of the wall of the uterus at this site. The operation was followed by incontinence of urine and, in fact, a vesico-vaginal fistula. Nine months later she was referred to Hammersmith Hospital where a large fistula was found and a biopsy of its margins showed anaplastic carcinoma. A bilateral uretero-colic transplantation with subsequent radium needling to the recurrent growth was considered to be the treatment of choice. The ureteric anastomosis was carried out with great difficulty: the patient was obese and the ureters were bound down to the posterior abdominal wall by peri-ureteric fibrosis—a not uncommon sequel to extensive irradiation in the pelvis. The pelvic meso-colon was short and swollen with fat, and the appendices epiploicae of the sigmoid colon were enormous. Nevertheless, the operation was completed and the convalescence was reasonably smooth: a temporary leak of urine occurred from the abdominal drain tracks but she was discharged home after 6 weeks, grateful that her urinary incontinence had been cured. A letter from her general practitioner reads "she has had 5 very comfortable months at home with her family getting up and about in the house but the pelvic growth has extended downwards and she has developed recurrent vaginal bleeding and discharge. At no time has she had any trouble voiding urine from the bowel."

Such surgical treatment is frequently only palliative but is a boon for the patient and justifies the efforts of the surgeon.

Utero-vesical Fistula

A fistula between the uterus and bladder is rare.

Case 4

R.C., aged 29 years, was successfully delivered of a child by a lower segment Caesarean section. Some blood-stained urine was noted 2 days after the operation and urinary incontinence developed within a week. She reported 6 months later with a story that she menstruated through the urethra and passed urine through the vagina. Examination under anaesthesia showed that urine leaked through the cervix and cystoscopy showed a well-defined fistulous opening in the bladder base approximately 2 cm. above and behind the right ureteric orifice. A hysterogram (Fig. 5) confirmed the presence of a fistula between the uterus and the bladder. Operation was advised and the fistula was excised through a combined transvesical and trans-peritoneal approach: the gap in the uterus was closed with interrupted catgut sutures, the bladder was reconstituted, a free omental graft was placed between the uterus and bladder and an indwelling urethral Foley catheter was used to drain the bladder for 7 days. The patient made an uninterrupted recovery and was discharged home after 2 weeks: she has remained symptom-free.

Vesico-colic Fistula

The commonest causes of fistula between the bladder and colon are diverticulitis and carcinoma of the colon but a vesico-colic fistula may follow gynaecological surgery.

Case 5

M.H., aged 37 years, was treated in 1954 for an anaplastic carcinoma of the vaginal vault. Three

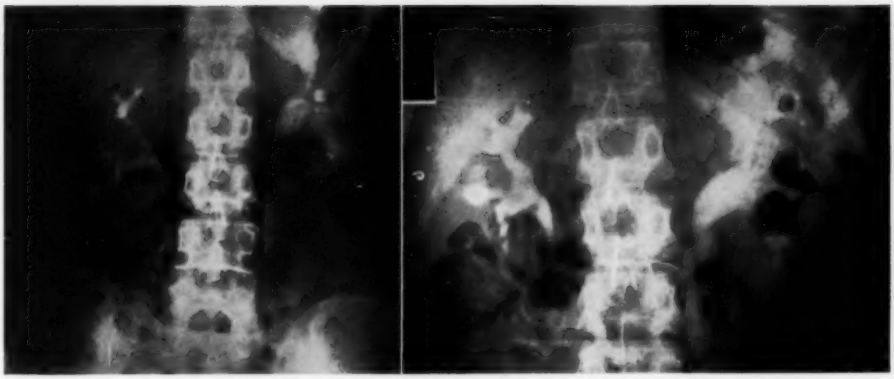

FIG. 1

(Case 1.) Excretion urograms showing a normal right kidney and left hydronephrosis and hydroureter following transection of the left ureter and primary uretero-ureteric anastomosis two weeks previously.

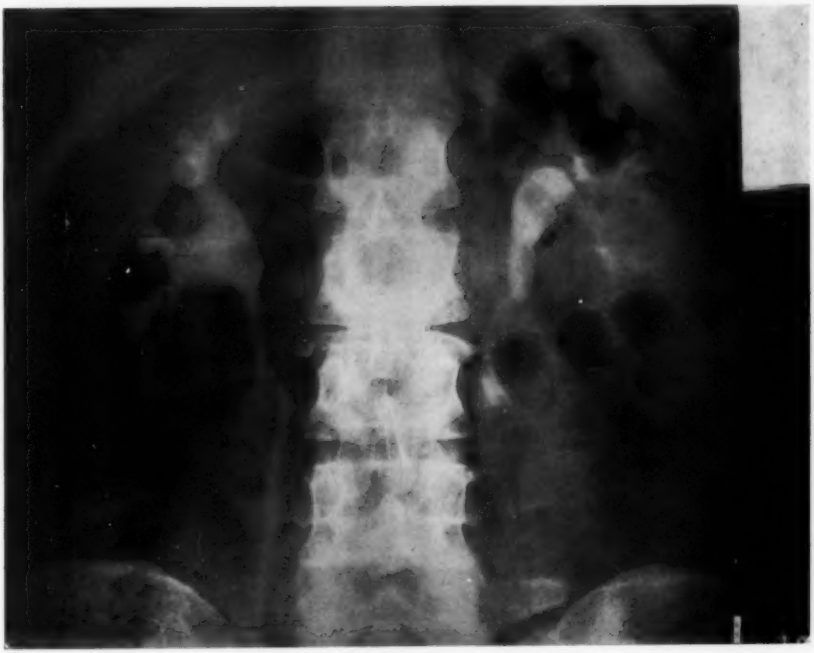

FIG. 2

(Case 1.) Excretion urogram showing restitution of the left hydronephrosis but still some degree of dilatation of the left ureter twelve weeks after uretero-ureteric anastomosis.

FIG. 3

(Case 2.) Excretion urogram showing a normal right kidney and left hydronephrosis following transection of the left ureter eight days previously.

FIG. 4

(Case 2.) Excretion urogram showing a normal left kidney fourteen weeks after re-implantation of the divided left ureter into the bladder.

FIG. 5

(Case 4.) Utero-vesical fistula. Radiograph showing radio-opaque contrast medium in the bladder after hysterography.

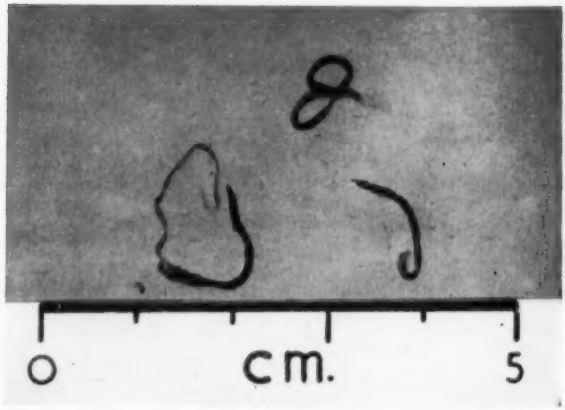

FIG. 6

(Case 7.) Catgut suture material removed at operation from the juxta-vesical portion of the left ureter 28 days after hysterectomy.

R.S.

FIGS. 7 AND 8

Retrograde pyelograms, lateral and antero-posterior views, showing ureteric kinking with obstruction at the pelvi-ureteric junction due to metastases from carcinoma of the cervix.

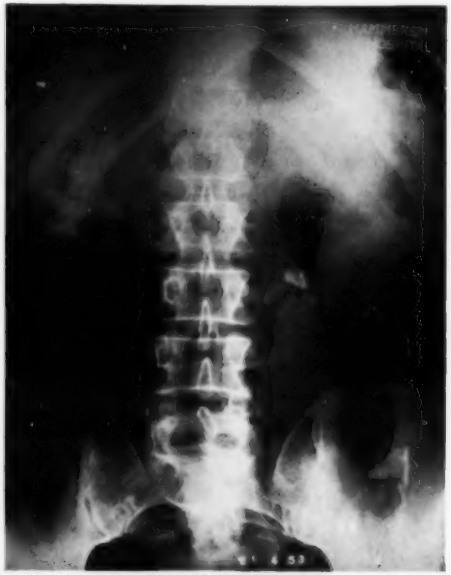

FIG. 9

Spontaneous gas pyelogram after direct end-to-side anastomosis of the left ureter to the sigmoid colon without a Coffey tunnel.

FIG. 12

(Case 12.) The lower abdomen of a patient with a left inguinal colostomy and an "ileal bladder" in the right inguinal region after total pelvic evisceration for recto-vaginal septum sarcoma.

applications of radium were followed, a month later, by a modified posterior exenteration: the rectum was excised together with the pelvic organs, and large bowel continuity was restored by a "pull through" procedure. Her convalescence was complicated by the development of a faecal and urine leak from the vaginal remnant and a transverse colostomy was carried out 3 weeks later. The perineal leak of urine persisted and a right ureterovaginal fistula was diagnosed and successfully treated 3 months after the exenteration by uretero-neo-cystostomy. Nine months later she developed an acute small bowel intestinal obstruction and was treated by enteroanastomosis with intraperitoneal isolation of a perforated loop of small intestine. This operation was followed by a suprapubic mucous sinus and a further attack of acute intestinal obstruction which required another laparotomy. Prolapse of the colostomy required yet a further operation and, 2 years after her first operation, an attempt was made to rid the patient of her suprapubic fistula by anastomosing the isolated loop of small bowel to functioning small bowel. However, a year later, she had 2 suprapubic sinuses through which discharged both urine and faeces. Excretion urography showed a right hydronephrosis. Right nephroureterectomy was carried out and cured the suprapubic urine leak. The suprapubic faecal leak was cured some weeks later by excision of the "isolated" loop of small bowel. A perineal leak of urine remained and a colpocleisis was undertaken but resulted only in a diversion of the urine from the perineum to the distal colon with leakage through the distal opening of the transverse colostomy.

Three more attempts were made to deal with the intolerable problem and finally the patient succumbed to a septic thrombosis of the inferior vena cava with pyaemic abscesses.

(*iii*) Spontaneous Deviation

Spontaneous deviation of urine may follow a vesico-vaginal fistula produced either by infiltrating malignant disease of the cervix and vagina or infiltrating tumours of the bladder: it may follow intracavitary irradiation (*vide infra*) or endoscopic diathermy. On occasion, the growth disappears as a result of treatment and a non-cancerous fistula persists but persistence of a fistula is sometimes evidence of persistent or recurrent growth.

Case 6

L.D., aged 47 years, was referred for treatment of irregular vaginal bleeding and urinary incontinence. A stage (IV) carcinoma of the cervix was found together with a large vesico-vaginal fistula. Biopsy confirmed the cancerous nature of the fistula. The blood urea was 130 mg. per cent and, not surprisingly, the excretion urograms failed to show any radio-opaque contrast medium. Bilateral uretero-colic transplantation was carried out and was followed by a course of radiotherapy by the linear accelerator some two months later. Pelvic exenteration was not advised. The patient returned to her home overseas with the urinary incontinence cured and one year later her condition was satisfactory.

Planned Deviation of Urine

Planned deviation of the urine in gynaecological surgery is usually performed as part of the surgical treatment of extensive malignant disease of the pelvic organs: when the malignant process has produced incomplete or early complete ureteric obstruction or when wide surgical excision of the pelvic organs is required and it becomes necessary to sacrifice the bladder. In such circumstances the urinary deviation is usually permanent. On occasion, however, urinary deviation may be only temporary.

Temporary Nephrostomy

Case 7

E.S., aged 40 years, underwent a hysterectomy for a fibroid uterus and developed anuria. When she was referred to Hammersmith Hospital one week later, the blood urea was 308 mg. per cent, the serum potassium 6·8 mEq/l, and the CO_2 combining power 13·0 mEq/l. Cystoscopy and ureteric catheterization confirmed that both ureters were completely obstructed 3 cm. above the uretero-vesical orifices. The patient was ill and it was decided to establish urinary drainage before seeking the cause of the obstruction. Accordingly, both kidneys were explored under general anaesthesia and were found to be tense and distended: bilateral nephrostomies were carried out. Adequate urine drainage followed this operation and the clinical and biochemical improvement was rapid: after 8 days, the blood urea had fallen to 34 mg. per cent, the serum potassium to 4·7 mEq/l, and the CO_2 combining power had risen to 28·0 mEq/l. The right ureteric obstruction subsequently underwent spontaneous resolution: the patient began to pass some urine naturally and the right loin ceased to drain. The obstruction to the left ureter, however, persisted and the left loin continued to leak urine: ureteric catheterization was repeated and confirmed the blockage noted at the previous endoscopy. The lower end of the left ureter was therefore explored through an extraperitoneal approach 3 weeks after the nephrostomy and a chromic catgut suture which had transfixed the juxta-vesical portion of the ureter was removed (Fig. 6). The subsequent course was entirely satisfactory and the patient was discharged home 3 weeks later passing urine naturally and with both nephrostomy wounds healed. Two months later, the excretion urograms showed normal renal function on both sides with no evidence of dilatation.

Case 8

F.W., aged 62 years, was treated by intracavitary radium for a stage (IV) carcinoma of the cervix. Cystoscopy at the time of the radium application showed bladder involvement: there was encroachment on both ureteric orifices. It was therefore no surprise when the patient subsequently became anuric and soon had a blood urea of 316 mg. per cent, a serum potassium of 6·6 mEq/l, and a CO_2 combining power of 15·7 mEq/l. She was desperately ill, not only with uraemia but also with an exacerbation of a chronic chest condition, and minimal surgery was advised. Since there was tenderness in the right loin and the right kidney was palpably enlarged, a right nephrostomy was carried out: the kidney was tense and distended. Adequate urine drainage followed this procedure and clinical and biochemical improvement were soon manifest: 3 weeks later she began to pass urine naturally and the nephrostomy tube was removed 6 weeks after its original insertion. Excretion urography then showed good function of the right kidney with minimal calyceal dilation: the left kidney showed no radio-opaque contrast medium. The uterine tumour at first responded well to the irradiation but the ultimate prognosis in such a case is clearly poor: indeed the right ureter soon became involved by "recurrent" tumour or post-irradiation fibrosis and renal failure developed again. The patient died a few months after the nephrostomy.

Permanent Nephrostomy

Permanent nephrostomy is not ideal for the self-retaining catheter has to be changed every few weeks—not always an easy procedure—and the patient has to wear a portable urinal. It is occasionally indicated.

Case 9

F.C., aged 54 years, underwent a laparotomy for carcinoma of the cervix in 1954. The condition was considered to be inoperable and she was treated by radiotherapy alone. Two years later, she underwent a right nephrectomy for a staghorn calculus and subsequently remained well for approximately 6 months. Then she developed malaise and vomiting, became comatose, and was found to have a blood urea of 240 mg. per cent and a blood pressure of 200/110. Obstruction of the left ureter was diagnosed and left ureteric catheterization was attempted. The catheter passed without much difficulty and the diagnosis remained obscure. The patient became anuric and was referred to Hammersmith Hospital with the blood urea 400 mg. per cent, the serum potassium 6·0 mEq/l, and the CO_2 combining power 14·8 mEq/l. Cystoscopy and ureteric catheterization was repeated and it was clear that the pelvi-ureteric junction had been displaced forwards by a soft tissue mass and that ureteric kinking at this site was responsible for the obstruction and the anuria (Figs. 7, 8). Left nephrostomy was immediately performed under general anaesthesia. Three weeks later the blood urea had become 24 mg. per cent, the serum potassium 3·8 mEq/l, and the CO_2 combining power 28·6 mEq/l. The site of the pelvi-ureteric obstruction was subsequently explored with a hope that the obstruction could be relieved: this, however, proved to be impossible and the patient was left with a permanent nephrostomy. Six months after her anuric phase she was relatively well and complained only about the inconvenience of the nephrostomy but she died 3 months later with widespread malignant metastases and thrombosis of the inferior vena cava: the kidney looked healthy at post-mortem.

Transplantation of the Ureters

Transplantation of the ureters into the colon has been a well-recognized surgical technique for planned deviation of the urine for at least 50 years and Grey Turner (1936, 1946) and others have recorded many successful cases. These operations, however, were carried out in the main for the treatment of congenital abnormalities such as ectopia vesicae or epispadias and it was necessary to await the advances in blood transfusion and anaesthesia and better understanding of fluid and electrolyte balance before the technique could be reasonably applied to cases of malignant disease.

Grey Turner employed the Coffey I operation (1928) and there can be little doubt that one of its principles, the submucous tunnel, has stood the test of time. Many patients more than 20 years after this type of transplant testify by their excellent general health and good renal function: some female patients have subsequently borne children without ill effect. Animal experiments (Shackman, Daniel and Lennox, 1952) have confirmed that ureteric reflux of bowel content or gas should not occur when a Coffey tunnel is used: in contrast, spontaneous gas pyelograms suggest the risks incurred by its omission (Fig. 9).

Nowadays it is recognized (Jacobs and Stirling, 1952) that the best technique is an end-to-side mucosa-to-mucosa anastomosis in combination with a submucous tunnel (Fig. 10): those methods which expose a free length of ureter to the bacteria of the colon are to be avoided. The end of the ureter should be sectioned obliquely so that a wide junction may be made and approximately eight interrupted sutures of 4/0 arterial silk are used for the anastomosis. A single layer of sutures is

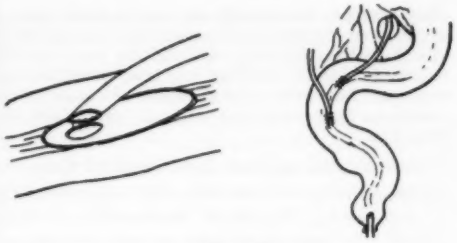

FIG. 10

End-to-side uretero-colic anastomosis. Interrupted 4/0 black silk arterial sutures are used for the mucosa to mucosal layer and also to approximate the edges of the serosa and muscularis of the Coffey tunnel. The right ureter is anastomosed to the upper part of the rectum while the left is brought through the sigmoid mesocolon and anastomosed to the apex of the sigmoid loop.

adequate and it is more important to avoid oversuturing, with the risk of devascularization, than it is to avoid a potential leak of urine: in any case, the closure of the outer thickness of the bowel over the ureter—the Coffey tunnel—also completed by a single row of interrupted 4/0 arterial silk sutures, reinforces the anastomosis. Four important points are worth emphasis (Fig. 11): the ureter should not be stripped of its fibro-fatty sheath and should be handled with maximal care to avoid devascularization, the ureter should not be angulated or taut, the submucous tunnel should loosely envelop the ureter and it is advisable to prepare a long and wide submucous bed at least 4×2 cm., and Penrose drains should be placed through counter-incisions and should remain in place for at least a week. A temporary leak of urine does not matter and usually ceases after removal of the drains provided there is no obstruction at the site of the anastomosis: risk of wound dehiscence is minimal when the drains are brought out through counter-incisions in the iliac fossae. The left ureter should be brought up through the sigmoid mesocolon before it is transplanted into the apex of the sigmoid loop a few centimetres above the right transplant and a rectal tube is always inserted, fixed by perianal skin sutures, and left in place for 5 days.

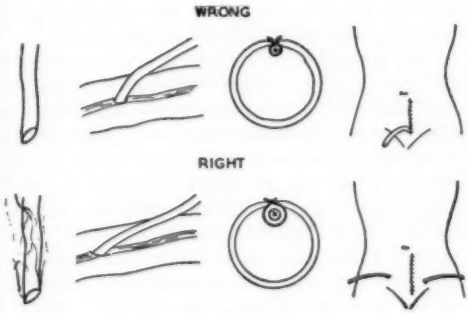

FIG. 11

Uretero-colic anastomosis. The top row, in contradistinction to the bottom, shows points of technique to avoid: these are (*i*) stripping the ureter of its connective tissue coat and blood vessels, (*ii*) angulating the ureter, (*iii*) too tight envelopment of the submucous tunnel around the ureter, (*iv*) drainage through the laparotomy incision.

Bilateral uretero-colic transplantation done carefully by this technique (Leadbetter, 1951) may take 2 hours to complete and, although it is not generally associated with any significant degree of operative shock and blood loss, it is wise to complete the urinary deviation at one stage and excisional surgery 3 or 4 weeks later: clinical and laboratory observations suggest that there is less "stress response" to staged operative procedures.

Case 10

S.C., a child of 4 years, was first seen in May, 1947 when the parents brought her to hospital because she had vaginal bleeding. Biopsy of an oedematous proliferative vaginal tumour showed sarcoma botryoides. Bilateral ureteric-colic transplantation was carried out as a prelude, 1 month later, to an anterior exenteration completed from the perineum when the pubic ramus, bladder, vagina and uterus were removed *en bloc*. Now, over 10 years later, the child is well with no evidence of recurrent tumour.

On occasion, there is a place for an emergency uretero-colic anastomosis.

Case 11

D.E.S., aged 37 years, had a subtotal hysterectomy for fibroids when she was 32. Three years later she was found to have a carcinoma in the cervical stump and was treated by a Wertheim operation. A recurrent mass in the pelvis was irradiated a year later and 6 months after this she developed a cough and haemoptysis due

to pulmonary tuberculosis. A pneumoperitoneum was carried out and she was given tuberculo-static drugs. After 2 months she became anuric and was transferred to Hammersmith Hospital with the blood urea 190 mg. per cent, the serum potassium 6·1 mEq/l, and the CO_2 combining power 9·5 mEq/l. She was desperately ill and was noted to have enlarged hard nodes in the left groin. Cystoscopy and ureteric catheterization demonstrated an impassable ureteric obstruction on the right side but a fine catheter could be passed the whole length of the left ureter. A unilateral low spinal anaesthetic was given and an extraperitoneal left uretero-colic transplantation was carried out: the ureter was 1 cm. in diameter and was obstructed by a fibrous mass just proximal to the bladder. Her recovery was rapid and she walked to the ambulance to go home on the 18th post-operative day with the blood urea 25 mg. per cent, the potassium 5·3 mEq/l, and the CO_2 combining power 28 mEq/l. A letter from her doctor some months later stated that her general health was deteriorating but that she voided urine without difficulty.

When excisional surgery is limited to an anterior exenteration uretero-colic transplantation is usually advised. When the rectum has also to be sacrificed, it is necessary to transplant the ureters into an isolated segment of small bowel and to form a wet ileostomy. The term "ileal bladder" is not strictly accurate because the urine drains freely to the exterior: indeed it should be encouraged to do so to prevent excessive reabsorption of nitrogenous and mineral substances. The isolated ileal segment is really a conduit to the exterior and is not a significant reservoir. Uretero-ileal transplantation implies the isolation of an ileal segment and transplantation of the ureters into the isolated bowel. And like the operation of uretero-colic transplantation it demands a careful technique and requires a significant time for its completion. For this reason it is safer to deviate the urine at one stage and to carry out the exenteration some weeks later.

Case 12

E.W., aged 68 years, was treated in 1925 for a sarcoma of the recto-vaginal septum. A left inguinal colostomy was carried out, radium needles were inserted into the tumour, and radium applicators were placed in the rectum and vagina. In 1950 she attended Hammersmith Hospital and was found to have an indurated stricture of the lower rectum: biopsy showed post-irradiation necrosis. In 1955 she developed incontinence of urine and was found to have a fistula which extended from the rectum across the vault of the vagina into the base of the bladder. Bilateral uretero-ileostomy (ileal bladder) was carried out and 6 weeks later a synchronous combined pelvic evisceration was completed. Histological examination confirmed the non-cancerous nature of the lesion. Seen one year later, the patient was well apart from arthritis of the spine: she manages her colostomy and ileostomy without much difficulty (Fig. 12).

The isolated segment is constructed from the distal ileum and should be approximately 25 cm. long. The distal transection is made about 10 cm. proximal to the ileo-caecal junction so that the restoration of bowel continuity is technically easy: when the transection is made too close to the ileo-caecal junction the bowel anastomosis may be difficult. The mesentery is divided at bloodless sites and care is taken to avoid devascularization of the bowel: the division should start at the margin of the bowel and continue down into the mesentery for not more than 6 cm. Intestinal clamps remain in position on the isolated segment until the bowel continuity is re-established, cephaled to the isolated segment, by an end-to-end or side-to-side anastomosis: an end-to-end reconstruction with 2 layers of continuous catgut is advised. The clamps on the isolated segment are temporarily removed and the segment of bowel aspirated and emptied: the distal clamp is then replaced and the proximal end of the segment is closed by 2 continuous catgut sutures. A few interrupted sutures are required to close the gap in the mesentery and prevent subsequent internal incarceration.

The technique for implantation of the ureters into the isolated segment should be the same as that described for uretero-colic anastomosis. Simple insertion (Brunschwig and Pierce, 1951) or direct anastomosis without a Coffey tunnel (Pyrah, 1956) are no doubt adequate in some cases but the intraluminal pressure in an isolated ileal segment may be significant and ureteric reflux may occur if the Coffey valve is omitted: and since bacteriological examination of the contents of an "ileal bladder" shortly after operation yields organisms comparable to those found in the colon after uretero-colic anastomosis the risk of ascending infection in such circumstances is not eliminated.

When the uretero-ileal anastomosis has been completed, the isolated bowel is anchored by a few interrupted catgut sutures to the posterior

and right lateral abdominal wall above the pelvic brim and its distal end is brought out through a counter incision in the right iliac fossa: approximately 3 cm. should protrude so that a small glass Paul's tube may be tied in and used to conduct the urine through light latex tubing to a sealed bottle. There is no need to anchor the protruding bowel to the parietal peritoneum for there is little risk of retraction if an adequate segment has been prepared: indeed such sutures may cut out and prove a nidus for peritoneal infection.

It has been suggested (Wells, 1956; Annis, 1956) that uretero-ileostomy is preferable to uretero-colic anastomosis on the grounds that ascending infection and hyperchloremic acidosis, admittedly potential sequelae of uretero-colic anastomosis, are less likely to follow uretero-ileal anastomosis. In fact, however, hyperchloremic acidosis is now of little import for it can be prevented by a low salt intake and daily oral ingestion of potassium citrate, while the risk of ascending infection is not eliminated in uretero-ileostomy since the bacterial flora of the ileal segment rapidly becomes similar to that of the colon. One thing is certain: in contrast to the patient with a uretero-colic transplant who can enjoy the social amenities of a normal person, the patient with an "ileal bladder" is handicapped despite the improved appliances now available for urine collection. For this reason, uretero-ileostomy should be carried out only if there is no alternative: uretero-colic transplantation, when possible, is to be preferred.

Acknowledgments

The author is indebted to his gynaecological colleagues, particularly Professor J. C. McClure Browne, Mr. Duncan Murdoch, and Mr. A. Starritt, for permission to treat and quote some of the cases. It is a pleasure to record evidence of close co-operation between the Gynaecologist and the Urologist.

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OVARIAN CHANGES CONCERNED WITH GONADOTROPHIC DYSFUNCTION AND ASSOCIATED WITH AMENORRHOEA AND INFERTILITY

TREATMENT BY OVARIAN WEDGE RESECTION AND EVERSION WITH GILLIAM SUSPENSION

BY

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SINCE my communication on the operation of extroversion of the ovaries for functional amenorrhoea, especially of the secondary type (Bailey, 1937), I have continued to treat selected cases by this operative technique with very satisfactory results, and have become convinced of the need for this operation in such cases which fail to respond to alternative therapy.

In America, Stein and his associates have continued to publish at regular intervals, and communications have appeared from them in 1935, 1939, 1945, 1949, 1955, 1957 and 1958. As a result of this stimulus, many other authors in the U.S.A. have also contributed to the subject during these years—notably Siegler (1944), Ingersoll and McDermott (1950), Meaker (1950) and Leventhal and Cohen (1951). As the result of this increasing interest shown by American gynaecologists during the last 20 years in this clinically important and quite baffling syndrome, it appears to be recognized by them now as an accepted clinico-pathological syndrome—the Stein-Leventhal syndrome—and amongst American gynaecologists the treatment of cases in this group by wedge resection of the ovaries has also come to be accepted.

In this communication I am able to present the details of a further 46 cases—to make a total of 63. In all of these there is a lack of ovarian function, absence of follicle ripening and ovulation, often some degree of uterine atrophy, menstrual irregularity chiefly featuring amenorrhoea and commonly associated infertility.

In the main, my cases conform clinically and pathologically to the Stein-Leventhal syndrome, but I have found that more retrogressive changes can occur in these ovaries in conjunction with the same symptom complex, and in my view as the result of the same aetiological factor.

I consider the problem to be best appreciated by the practising gynaecologist who is in a position to correlate the clinical symptoms and examination with the pathological condition of the uterus, endometrium and ovaries as seen at operation. Thus far the assistance to be gained from hormone assay estimation has been disappointing.

The object of this communication therefore is:

(1) To indicate the range of ovarian changes possible in association with the clinical aspects of this syndrome and its aetiology.

(2) To further stress the logical nature of the operation of ovarian eversion combined with Gilliam Suspension in the treatment.

AETIOLOGY

My view of the aetiology differs to some extent from that of other authors, and the rationale of my operative technique depends on it.

Stein and Leventhal (1935) have contended that increased anterior pituitary gland secretion accounts for the syndrome and that crowding

of the ovarian stroma by cysts prevents follicle development.

In my 1937 communication I said that in these cases "I have presumed a pathological change to have occurred in the ovaries as the result of the presence of a basic pituitary hormone deficiency resulting in their secondary cessation of function. Lack of follicular ripening and ovulation appears to lead to the development of a condition of multicystic disease in the ovaries, or, alternatively, and to a lesser degree in my experience, a state of chronic cirrhosis of the tunica with progressive fibrosis of the ovarian stroma."

Ingersoll and McDermott (1950) demonstrated the normal character of the hormone assays in 21 cases, and suggested that a collagenous infiltration of the ovarian capsule might be the basic disorder. Androgenic activity has been attributed by Greene and Burrill (1939) to excess progesterone production and, by Deanesly (1938), to luteinization in the theca interna.

Certain authors consider that luteinizing hormone is diminished in production and effect in this condition. Thus Fischer and Riley (1952) assert that "Progesterone inhibits ovulation by inhibiting the production of luteinizing hormone by the pituitary" and Evans and Riley (1958) say "not only does an absence of sudden increase in oestrogen inhibit release of adequate L.H. . . .".

Again other authors consider that luteinizing hormone is an active factor. Thus Greenblatt (1953) states that "Excess pituitary stimulation of the ovaries probably by luteinizing hormone may produce the hyperthecosis so frequently seen". Again Greep *et al.* (1942) showed the effect of luteinizing hormone on hypertrophy of the interstitial cells of the theca, and Pfeiffer (1941) demonstrated its effect on thecal luteinization and masculinization. Haas and Riley (1955) feel that follicle development begins normally, but that there is "something lacking to complete the ovulatory process". More recently Leventhal (1958) has stated that "The role of F.S.H. is not clarified, but evidence points to the excessive secretion of L.H. as a causative factor". An anatomical approach was provided by Reynolds (1947) who stated that the blood pressure in the terminal arterioles of the ovary is controlled by spiralling and that the spiralled arterioles become straightened under certain conditions of gonadotrophic control, thus causing a transudation of fluid into the follicles with the production of cysts.

Shippel (1955) in his pathological survey first of all tilts at the view that "the theory of bilateral polycystic ovaries has invariably been sought in the pituitary", and seeks to show that the androgen-producing effect of the ovarian theca cell is the primary cause. He states that "the primary aetiology of this syndrome is not abnormal or excessive pituitary stimulation of the ovaries—the usually accepted explanation—but rather factors inherent in or locally irritative to the ovaries . . .". Later in his communication, however, he states that "As the hormone production of the ovarian follicle increases so pituitary function is depressed. This inverse relationship between the ovarian and pituitary functions results in phases of follicle stimulation and follicle depression and atresia. During these phases some thecal hyperplasia *may occur* —and *may be marked.*" By this statement not only is the pituitary influence admitted, but also the initiation of marked thecal hyperplasia is presumed out of context with pituitary imbalance. From this point Shippel contends that "as this theca increases, so does its capacity to depress the pituitary increase, with the result that the amount of gonadotrophin necessary for the stimulation of primordial follicles to maturity slowly becomes unattainable".

Shippel, therefore, whose pathological work is based upon the examination of laboratory specimens removed at operation, attempts to make the ovary itself the primary controlling agent in a widespread dysfunctional state, of which he says that the Stein-Leventhal syndrome is but "an end result". Whilst agreeing that the Stein-Leventhal syndrome does form only a part of a wide gonadotrophic dysfunction, I cannot presume with him that this end-organ of the hormonal chain is the primary initiator. I would rather suggest that the marked or excessive thecal hyperplasia which may occur does so as the result of higher influences.

Many possible aetiological factors have been advanced, but none have suggested a probable

pituitary gonadotrophic hypofunction. This, however, is what I believe to fit most accurately the clinical and pathological pictures presented. It is upon this that I base my own view.

I have always presumed the soundness of the original view of Novak (1921), who said that "Ovarian dysfunction is most often an ovarian reflection of disordered function of the anterior pituitary", and I have always believed in the work of such authorities as Foster and Fevold (1938), who showed that "ovulation depends on the synergistic interactions of the follicle-stimulating and luteinizing factors which must bear a definite quantitative relationship to each other—should this relationship be disturbed, the ovulation-inducing efficiency is markedly diminished". Again Simpson and Evans (1940), in conformity with the view of Foster and Fevold, maintain that "the luteinizing factor exists as a distinct principle and possesses specific physiological properties, namely to stimulate the interstitial tissues . . .".

I would suggest that the ovarian changes seen in my cases are essentially retrogressive in nature and possibly due to a quantitative (and possibly qualitative) under-production of both follicle-stimulating hormone and luteinizing hormone acting over a long period of time, but with a progressive predominance of luteinizing hormone over follicle-stimulating hormone as the total amount of production is lessened.

This belief is based upon the facts that: (1) the endometrial development in the majority of my cases is below normal, except in the earlier type of case where proliferation is present. In fact, in many cases, the endometrium on curettage has been extremely scanty or absent. There has been no secretory phase. (2) In a number of the cases there has been macroscopic evidence of a degree of uterine atrophy. (3) The cystic ovarian follicles show development up to a point only, with early cystic atresia, and the granulosa layer is underdeveloped, and (4) the theca interna is relatively hyperplastic throughout the phases of retrogression.

I consider therefore that a diminished follicle-stimulating hormone production leads to this incomplete follicle development and early atresia, and the relative predominance of luteinizing hormone leads to the hyperplasia of the interstitial cell-layer. This hypofunction and imbalance is so slight as to leave unaffected the results of hormone assays as at present estimated—as to have little or no effect upon the general health and metabolism of the majority of affected patients—and as to manifest itself clinically only in the production of menstrual disturbance and associated infertility —and pathologically in the production of the polycystic state.

If for instance the normal balance between follicle-stimulating hormone and luteinizing hormone production were in the ratio of 100 to 1 —in the case of the polycystic ovary, where the imbalance is relatively minor (say follicle-stimulating hormone 75–luteinizing hormone 1), the follicle is incompletely developed and fails to combine fully with the effects of luteinizing hormone for maturation. Cystic atresia is prematurely initiated in conjunction with over-stimulation of the theca interna and tunica. Full maturation is prevented and the typical multi-cystic change becomes established. This may be called the early imbalance phase. As the quantitative production becomes less (say follicle-stimulating hormone 50, luteinizing hormone ·9), and the luteinizing hormone dominance increases (or if this be initially present), the follicles become less developed still, and the interstitial tissue more established —as in cirrhotico-cystic change, the intermediate imbalance phase—thus leading to cystic and cirrhotic ovarian atrophy (say follicle-stimulating hormone 25, luteinizing hormone ·5)—the late imbalance phase.

This is, of course, merely a theoretical consideration—based upon the clinical evidence and the ovarian changes observed. The majority of cases, of course, remain in the first category of polycystic change, which indicates the commoner minor degree of pituitary hypofunction.

With regard to the aetiological factor, therefore, I feel that the polycystic changes, and the cirrhosis of the tunica and stroma represent a slow but progressive retrogressive phase, resulting from this lack of hormone supply, which if not readjusted will progress to final ovarian failure, as the result of the total destruction of all potential follicles and stromal

cells within the ovarian structure. In my observation of this syndrome over the last 25 years, I have constantly noticed the progressive functional deterioration exhibited by these patients—their progressive failure in the degree to which they can react to the effect of hormonal replacement therapy. It is impossible for me to assert, however, that those few cases of my series which demonstrated a more cirrhotic or atrophic ovarian state have actually passed through the polycystic phase. It may be that the degree of pituitary hypofunction and imbalance in these cases has been initiated *de novo*, and that the resultant ovarian change has progressed rapidly to this state. As a secondary factor in the aetiology, I feel that the opinion of Reynolds (1947) might be relevant. In some of what I consider to be the earlier cases there is evidence at operation of the presence of numerous fine arterioles close to the ovarian surface—an appearance which suggests the probability of increased arterial pressure in the main peripheral arteries, which Reynolds said lost their spiralling under certain conditions of gonadotrophic control. Moreover there is some evidence in these cases of a degree of diffuse fluid transudation in the stromal tissues, which suggests the effect of such hyperaemia. I rather think, therefore, that this condition might possibly result from the pituitary dysfunction which I have suggested as the primary aetiological factor, and might represent a transitory phase.

Longitudinal Studies of Gonadotrophic Excretion in the Stein-Leventhal Syndrome

In a communication on longitudinal studies of gonadotrophic excretion in the Stein-Leventhal syndrome, Ingersoll (1959) undertakes the measurement of the urinary excretion of ICSH in the Stein-Leventhal syndrome, as a result of the development in the laboratory at the Harvard Medical School of a biological method for measuring this factor.

Many of the results of investigations reported by Ingersoll appear to be inconclusive from the point of view of throwing direct light upon the aetiology. Ingersoll in mentioning the theory postulated by me in 1937 says that in 1950 he suggested that this "might involve more specifically a deficiency of ICSH". In this present communication I suggest that this is so but that there remains a relative preponderance of ICSH over FSH due to a more pronounced deficiency of the latter, and that as this becomes more pronounced the ovarian pathology changes to the more cirrhotic and atrophic. Ingersoll does say, however, that "there are also good reasons for believing that there may be an excess of ICSH in this syndrome", and quotes the work of Keettel and co-workers in demonstrating this.

Ingersoll comments that "the classical experiments in reproductive physiology have demonstrated that ovulation occurs only when gonadotrophic stimulation of *adequate intensity* and duration is applied to a properly primed follicle". This opinion of his based upon these intricate experiments I can fully agree with, from the purely pathological and clinical observations from which my own views are deduced.

Pathology

With regard to the ovarian pathology, American authors recognize particularly a single type of ovary concerned with this syndrome—the multicystic type with pearly white thickened tunica, containing possibly partially developed Graaffian follicles (Stein and Cohen, 1939; Ingersoll and McDermott, 1950; Leventhal and Cohen, 1951).

Shippel (1955) in his attempt to prove the gradual dominance of the thecal elements, divides his cases into 6 phases—the first 3 representing stages of the Theca Granulosal synergistic phase and the last 3 representing phases of the Thecal Dominant phase. Some of his cases are in the fifth and sixth decade of life. Some have uterine fibroids and ovarian tumours. Shippel's material therefore goes beyond the clinical group with which I am concerned—the third decade in which the problem of infertility is a main factor.

The Early Imbalance Phase

In my own series, therefore, I have seen most frequently the type of hyperplastic polycystic

ovary described by Stein and others, with the typical smooth bluish white thickened tunica. In the earlier types exhibiting arterial tension, I have also noted a diffuse fleshy appearance, due to a combination of hyperaemia and serous effusion (as mentioned by Reynolds, 1947). In these cases the uterus might show some degree of atrophic change, being reduced in size and thickness. The endometrium may be somewhat proliferative or scanty, with no secretory phase. Histologically, the ovary shows the typical thickened tunica with many cystic atretic follicles lined by thin granulosa layers and relatively thick theca layers. There is evidence of swollen stroma cells and fluid transudation with hyperaemia.

The Intermediate Imbalance Phase

There has also been present to a lesser degree in these cases the ovary which exhibits much more markedly the cirrhotic to the exclusion of the cystic change. This cirrhosis differs from the smooth collagenous surface seen in the polycystic type, and varies from a localized plaque of thickened corrugation of the tunica on the surface of a multicystic ovary (cirrhotico-cystic), to a diffuse cirrhosis which involves the majority of the ovarian structure and ultimately transforms the ovary into a hard corrugated mass with the destruction of most of the cortical tissue. Deep seated cystic follicles are relatively few and lined by a single row of cells. Potential developing follicles are therefore reduced to a minimum in such ovaries. In these cases also there is an associated degree of uterine and endometrial atrophy. The uterus usually measures 2 to 2½ inches in length, and is thin walled and lacking in muscle elements. The endometrium is absent or scanty. This stage therefore represents a pathological transition between the earlier polycystic reaction and a more retrogressive cirrhotic change—and this stage is also encountered clinically. Here the generalized collagenous infiltration and fibrosis of the interstitial cell tissues has become complete. The ovaries are densely hard, diminished in size and heavily corrugated. The follicles are few and small. The functional potential is much diminished.

The Late Imbalance Phase

Again, in this clinical syndrome concerned with functional amenorrhoea and infertility, one occasionally encounters a condition of uniform and bilateral atrophy of the ovaries. In such cases the ovaries at operation are seen to be uniformly diminished in size—to about half or one-third the normal, and their substance is markedly diminished in amount. In some there is a degree of local cirrhosis of the tunica, or polycystic change (cirrhotic or cystic atrophy). There is some degree of surface flattening due to obliteration of the sulci, and there is no evidence of follicle ripening or a corpus luteum. I feel that this state might represent the ultimate result of diminished follicle-stimulating hormone and luteinizing hormone production and imbalance—wherein the hyperplastic effect of luteinizing hormone becomes negative. The uterus is atrophic and the endometrium absent or scanty.

In my series a few of these cases occur. Operation has been carried out because the amenorrhoea failed to respond to general and hormone therapy, and in the expectation of finding the cirrhotico-cystic type of ovary. In these cases the ovaries have been everted without wedge resection in the usual way, but it has been observed that their substance is uniformly attenuated and devoid of follicle potential.

In my experience, therefore, there have been 3 ovarian pathological types to be encountered in conjunction with this clinical syndrome, the polycystic change being by far the most common. In the majority of cases there is nothing in the patient's physical health or appearance to suggest gross hormonal change, beyond some degree of hirsutism or obesity. Only the amenorrhoea or epimenorrhoea and infertility indicate the inherent upset.

These three pathological changes, (1) diffuse polycystic change, (2) cirrhotico-cystic change, or diffuse cirrhosis, and (3) cirrhotico- or cystic atrophy, or diffuse atrophy, might possibly therefore stem from a varying degree of the same gonadotrophic upheaval. If this be so, the fascinating thing is to determine the factor which decrees the type of change (which I think is essentially retrogressive), to be brought about in different individuals. As has occurred in my series, it is possible for an apparently

FIG. 1

Early Imbalance Phase. (Mrs. M.) Age 28.

Typical bilateral polycystic ovaries of Stein-Leventhal type. Ovaries enlarged to +3—bluish white—sulci obliterated—uniformly thickened. Tunica—uniformly smooth surface. Uterus normal *or mildly* atrophic. Early luteinizing hormone dominance.

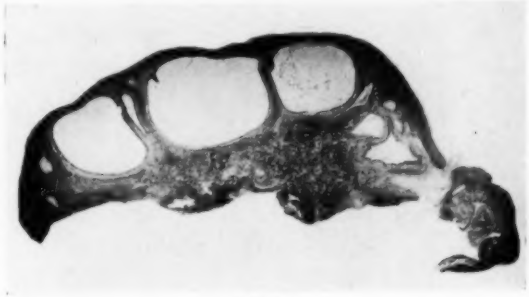

FIG. 2

Early Imbalance Phase. (Mrs. D.)

Cystic atretic follicles in ovarian cortex. Thickened tunica—a partly developed Graaffian follicle—thin granulosa layer—hypertrophied theca interna—commencing fibrosis of stromal tissues.

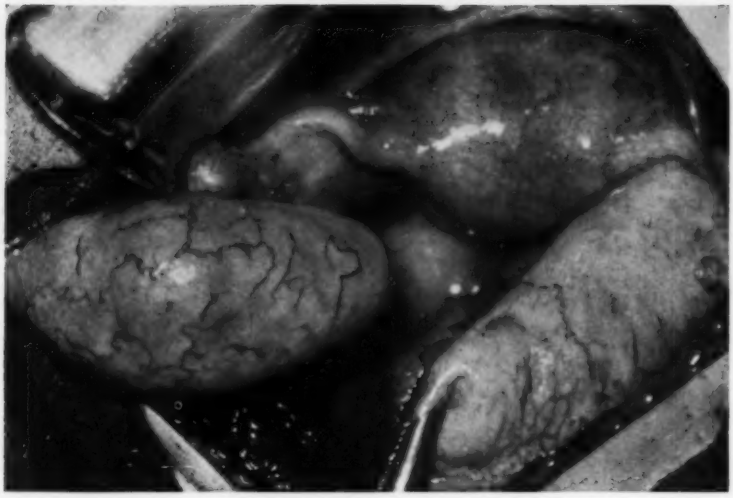

FIG. 3

Early Imbalance Phase. (Mrs. T.) Age 33.

The probable early transient phase which precedes diffuse polycystic change.

Ovaries enlarged to +4—generalized thickening of tunica—generalized arterial ramifications on ovarian surface due to increased tension (Reynolds). Commencing luteinizing hormone dominance.

FIG. 4

Early Transient Phase. (Mrs. T.)

Wedge removed from ovary showing: (I) Multicystic conditions of cortex. (II) A diffuse oedema due to effusion of serum into stromal tissues consequent upon arterial pressure.

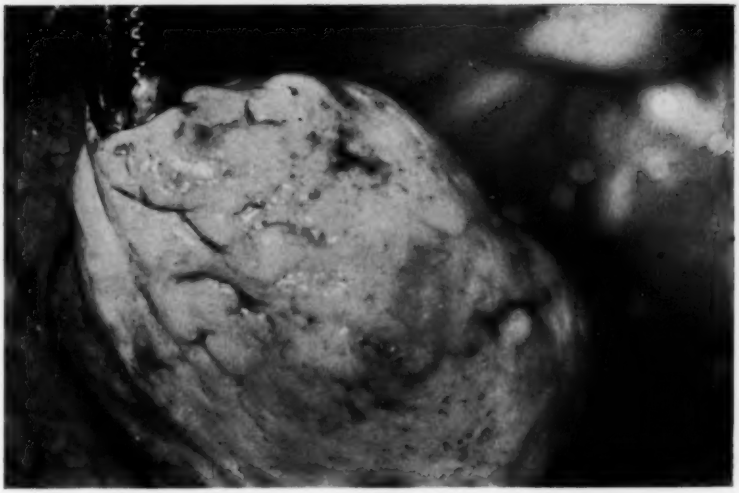

FIG. 5

Intermediate Imbalance Phase: Stage I. (Mrs. M.) Age 26.

The transition between polycystic and cirrhotic change. The ovary is largely polycystic but there is a large plaque of heavily cremated and collagenous thickened tunica at one pole. Increased luteinizing hormone dominance. Cirrhotico-cystic change.

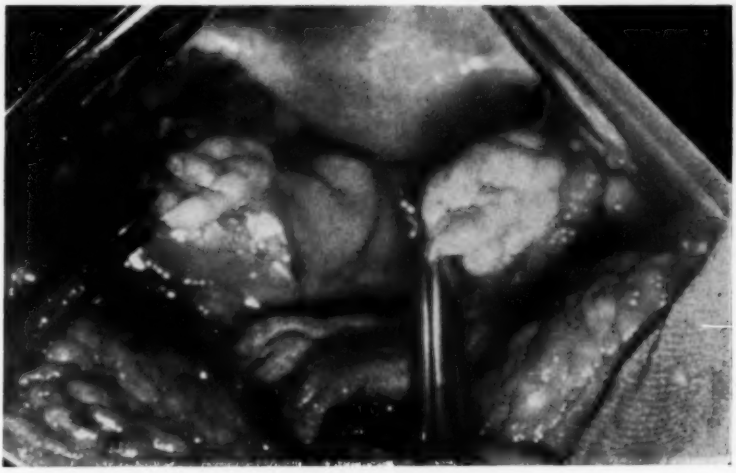

FIG. 6

Intermediate Imbalance Phase: Stage II. (Mrs. D.) Age 30.

Bilateral diffuse *cirrhosis* of ovaries. Diminished in size. Heavily corrugated. Diffuse cirrhosis. Few and *small* atretic follicles. Increased luteinizing hormone dominance.

FIG. 7

Intermediate Imbalance Phase. (Mrs. D.)

The generalized diffuse spreading collagenous infiltration of the tunica with fibrosis. Few small atretic follicles. Functional potential minimal.

FIG. 8

Late Imbalance Phase. (Mrs. B.) Age 21.

Bilateral cystic atrophy of ovaries. Both ovaries diminished to —3. Small cystic atretic follicles. Generalized diminished stromal tissues. Some diminution of sulci. Absolute luteinizing hormone dominance. Functional potential minimal.

K.V.B.

FIG. 9

(Mrs. B.) Age 21.

Ovaries seen at operation in Figure 8. Bilateral cystic atrophy. Late imbalance phase. Apart from mild obesity there is no gross physical or mental abnormality.

FIG. 10

(Mrs. M.) Age 26.

Ovary seen at operation in Figure 5. Intermediate imbalance phase. Cirrhotico-cystic ovary. No physical or mental abnormality. No hirsutism.

FIG. 11

Operation of wedge resection with eversion of the ovary. Stage I: Removal of thin wedge from cortex. The tendency of the thickened tunica to infold is dealt with by shaving off the edges.

FIG. 12

Ovarian eversion.

Stage II: The wedge is removed. The cystic cortex is exposed. The inverting tunica is demonstrated. This position is now fixed by two or three everting mattress sutures of 00 catgut.

FIG. 13

Ovarian eversion.

Stage III: The everted ovary is now completed by two 0 catgut sutures.

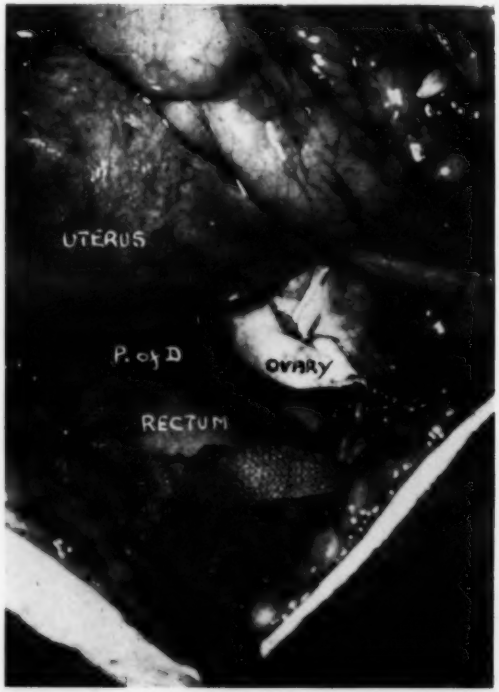

FIG. 14

Gilliam Suspension.

The essential Gilliam Suspension follows ovarian eversion. The ovaries are thus suspended above the pouch of Douglas. The exposed cut surface is thus out of contact with other surfaces. The tunica surface faces upwards.

normal woman of 25 to cease menstruating over a long period of time (after prodromal indications), and at operation the ovaries show uniform atrophy whereas, in other similar individuals with the same type of history, one or other of the above pathological changes are present. In all of these the hormone assays remain within normal limits, and there is no gross physical abnormality to be observed in many of them.

About 80 per cent of my cases show the presence of the polycystic type of ovary—which is to be expected in so far as this ovarian change is the one likely to result from the mildest form of imbalance—a functional state possible in women whose development has been normal, and whose function has been apparently normal until the early or middle twenties of life.

In my series, therefore, I have dealt with this type of case as the major clinico-pathological group, and have expressed my experience and treatment of it alongside that of American gynaecologists.

In addition, I should like to present the Stein-Leventhal syndrome as the major evidence of a more comprehensive hormonal upset resulting in further ovarian changes which are probably related to the degree of such upset.

Pathological Results

This series of 63 cases therefore are comprised of:

(1) 17 cases reported in 1937.
(2) 11 cases reported in 1946.
(3) 35 cases now added.

All these cases conform clinically to the syndrome—and in none of them was the presence of a Graaffian follicle or corpus luteum demonstrated at operation.

Of these 63 cases:

45 showed bilateral polycystic ovaries at operation.

4 showed polycystic change in one ovary, but a more cirrhotic change in the other.

10 showed a cirrhotic-cystic or diffuse cirrhotic change in both ovaries.

4 showed cystic or cirrhotic atrophy in both ovaries.

Clinical

Stein (1945) and Leventhal and Cohen (1951) report hirsutism in "about 50 per cent" of their series. Jackson and Dockerty (1957) in their series state that "The majority of these patients were obese, excessively hairy, hypertensive and infertile". In Meaker's (1950) series of 65 cases, hirsutism appears to have been a concomitant to the extent of about 50 per cent—and similarly in Siegler's (1944) series of 26 cases.

I have found in my series, however, that these general manifestations of obesity and hirsutism have not been by any means constant features. I have noted some 11 cases of hirsutism and 10 of gross obesity in the series. In 3 cases there was a definite loss in body weight. In fact, one might say that the majority of the 63 patients showed no outward and visible sign of abnormality, either physically, mentally or psychologically. They appeared therefore on the surface to be normal female individuals—affected, be it said, by the secondary stresses of their condition.

In Shippel's cases 10 show marked hirsutism, 12 show "increasing" hirsutism, and 5 show "commencing" hirsutism.

Prunty, Brooks and Mattingly (1958), in reporting a series of 44 cases of hirsutism, stated that the findings with regard to the Stein-Leventhal syndrome were not very definite.

I consider, therefore, that, since the effect of suprarenal hyperplasia cannot be demonstrated by definitely elevated 17-ketosteroids in conjunction with the syndrome which we are considering here, the association of hirsutism in some degree has probably been regarded as having greater significance than in fact it has. Neither has gross obesity shown itself to be a constant or marked factor in this series.

Apart, therefore, from the predominant symptom of functional amenorrhoea in these cases, there is no doubt that other dysfunctional symptoms present themselves also in or out of association with it. Thus a number of my cases have presented with irregular uterine bleeding of the anovular type, a few with menorrhagia, some with severe dysmenorrhoea, and some with established hypomenorrhoea over a long period of time. These symptoms I regard as dysfunctionally associated.

Pre-operative clinical features in 63 cases.

Functional amenorrhoea of more than 2 years in 6.

Functional amenorrhoea of more than 1 year in 8.

Functional amenorrhoea of more than 6 months in 15.

Irregular menstruation with hypomenorrhoea or menorrhagia in 16.

Severe dysmenorrhoea in 12.

Infertility (42 cases) in 26.

Diagnosis

The diagnosis of the typical case can be readily made from a consideration of the history, and the discovery on pelvic examination of the presence of grossly enlarged ovaries—usually to about the size of small walnuts. In addition, of course, much interest has been given in the past to the estimation of hormone assays, and in the U.S.A. gynaecologists also employ some form of gynaecography to assist diagnosis.

Haas and Riley (1955) reported all hormone assays to be within normal limits in their series—and it now appears to be generally accepted that these assays—as now assessed at any rate—are not indicative of the nature or clinical presence of this condition.

Stein advocates additional operative aids to diagnosis. Lately (1955), he has stated that "Bimanual examination is inconclusive in half my cases". He advises the use of culdoscopy, colpotomy, and gynaecography, including pneumoroentgenography and hysterosalpingography.

My decision to operate has always been based upon a consideration of the clinical aspects and examination, together with the complete failure to respond to prolonged general and hormone therapy. The pelvic examination is usually definite in cases of developed polycystic change in the ovaries, and often so in the case of cirrhosis. The need for laparotomy, however, is by this time established on clinical grounds alone—and as in some of these cases I expect to find one or other of the alternative conditions in the ovaries (atrophic, cirrhotico-cystic), which themselves often do not permit of definite clinical diagnosis. I feel that the question of laparotomy is not concerned with diagnosis at this stage, but with treatment.

Prior to laparotomy, a diagnostic curettage for biopsy of the endometrium should be carried out. In the established case, by this means the presence of a degree of uterine atrophy is assessed, and the absence of mature development of the endometrium is also discovered. In this respect, the endometrium has almost always indicated an underactivity of oestrogenic influence with lack of evidence of ovulation. I believe, therefore, that the endometrial biopsy should never be overlooked.

Treatment

As has been said, all forms of non-operative treatment are applied in these cases before laparotomy is resorted to. In my own series, it has been amply and reasonably proved that these have failed to re-establish ovarian function by ovulatory menstruation.

There is no doubt that the number of cases affected by the degree of ovarian dysfunction under consideration is small compared with those minor or less persistent ones which settle spontaneously or with medical treatment. The discriminative selection and recognition of these cases is the important matter.

Hormone therapy over the years has proved ineffective. Engle (1952) has stated that "with the gonadotrophic hormones at present at our command I have never been able to release one ovum from the human ovary", and according to Greenblatt (1953), even cortisone has been disappointing in the treatment of the syndrome. Some years ago Ingersoll and McDermott (1950) said that "once the diagnosis of fibrosis of the ovarian capsule with polycystic ovaries has been made there is no question but that the treatment is surgical", and more recently Jackson and Dockerty (1957), in their series of 43 cases, again stressed the normal results in hormone assays and conclude that "the most widely accepted therapeutic procedure consists of wedge resection of both ovaries as advocated by Stein and Leventhal". The report from the Mayo Clinic would therefore appear to establish

the recognition of the Stein-Leventhal syndrome, and also the surgical approach to it.

The Operation of Wedge Resection and Eversion of the Ovaries Combined with Gilliam Suspension

The fact of extroverting or everting the ovaries results in the deliberate formation of two raw surfaces, left *in situ*—a factor which, of course, runs counter to accepted tenets of surgical technique, and one which, when I first described it, called for criticism.

I initiated this technique, however, because having regard to the diminished gonadotrophic stimulus, I believe that the developing and potentially functional follicles which are situated in the deeper areas of the stroma can only be afforded a possible chance of maturation and surface rupture, if a new, more readily accessible and unobstructed surface is constructed in their immediate vicinity. The hazard of the raw surface—namely adhesion between the ovaries and peritoneum or omentum or intestine—is offset by preventing any possibility of contact between them and other structures by carrying out a Gilliam suspension, which results in their being suspended on the posterior aspect of the broad ligaments with their raw surfaces directed down and back and overlooking the cavity of the pouch of Douglas.

By this means, adhesion is prevented, and, in addition, any slight sero-haemorrhagic exudate from the cut surfaces is readily absorbed in the pouch of Douglas. I have constantly noted at follow-up, that the uterus and appendages remain in free anteversion and mobility—and I have on no occasion in my series had to re-open the abdomen for immediate or remote effects following this operation. In fact, I consider that the good functional results recorded are sufficient proof of the absence of any post-operative complications, such as could possibly militate against the free mobility of the pelvic organs—without which the normal function of menstruation and pregnancy could not obtain.

These factors I would suggest represent some improvement on the technique of pure wedge resection with closure, in which the possibility of (1) a re-establishment of the pathological *status quo* is made; (2) the prospect of post-operative inflammatory cyst formation in the ovarian stroma, due to lack of drainage is present; and (3) the likelihood of post-operative adhesions between the ovaries and pelvic peritoneum due to exudate and contact is a probability.

I have seen these ovaries on two occasions at Caesarean section, within a year of eversion. The cut surface was covered by a semi-transparent membrane, giving a glazed appearance and probably due to re-epithelialization by germinal epithelium.

Choice of Case

I cannot do better than repeat my opinion of 1937. I would assert that this operation is justifiable in the following cases:

(1) Where endocrine therapy alone fails to restore regular menstruation or something approaching this state.

(2) Where a lesion of the ovaries such as has been described can be detected clinically. The progressive nature of the lesion renders the outlook less and less favourable.

(3) Where time itself fails to rectify menstrual function and particularly where this dis-improves as time goes on.

(4) Where the nervous system shows signs of suffering in consequence of the amenorrhoea, and

(5) Where the factor of infertility is consequent upon the ovarian dysfunction.

Results of Operation

American gynaecologists claim extremely good results from their operation of wedge resection and re-suture of the ovaries. Thus:

Stein, Cohen and Elson (1949)—76 cases with 90 per cent to 100 per cent functional result and 66 per cent pregnancies.

Meaker (1950)—65 cases with 77 per cent functional and 66 per cent pregnancies.

Siegler (1944)—26 cases with 69 per cent pregnancies.

Ingersoll and McDermott (1950)—21 cases with 68 per cent restoration of function.

Ellett and Barnes (1957)—5 cases with 2 pregnancies.

Haas and Riley (1955)—7 cases with 68 per cent restoration.

Evans and Riley (1958)—19 cases with 16 pregnancies.

Clinical Results

At the time of presentation of the 1937 series, however, it was reported that normal menstruation was restored by operation in 13 of the 17 cases, and 1 full-term pregnancy had followed operation. The follow-up with regard to pregnancies in this series has not been possible.

In the 1946 series, regular menstruation was restored in 9 of the 11 cases, and 3 full-term pregnancies had occurred. Further follow-up in this series is not adequate.

In the additional series of 35 cases—22 have been operated upon long enough for long-term follow-up. In these 22 cases:

Regular menstruation was restored in 18 cases.

Irregular menstruation (5–9 weeks) was present in 3 cases.

Continuation of amenorrhoea in 1 case.

Eleven full-term pregnancies, and 1 three-months abortion occurred.

The precise follow-up in the total series with regard to the occurrence of pregnancy has therefore been inadequate, but sufficient evidence has been collected to show that satisfactory results can be obtained by operative means; and I agree with Stein and Leventhal and others, only by operative means in this type of case.

Case Reports

Brief details of 3 cases of this series are as follows:

(1) *A Case of Bilateral Polycystic Ovaries*—(80 per cent of the series are of this type)

Mrs. W. Aged 28 years. Menarche at 16.

Complains of infertility of 3-years duration, and alternating bouts of amenorrhoea and menorrhagia, the longest period of amenorrhoea being 5 months. Bled from October to December and has been amenorrhoeic since. No improvement with hormone therapy. Preliminary dilatation and curettage showed an atrophic uterus with extremely scanty curettings, probably insufficient for histology.

Laparotomy—showed bilateral polycystic ovaries. Wedge resection of both ovaries carried out followed by eversion and routine Gilliam suspension.

(2) *A Case of Cirrhotico-cystic Ovaries*

Mrs. M. (Fig. 10). Aged 25 years. Menarche at 12.

Complained of severe dysmenorrhoea, which had not been relieved by dilatation of the cervix. Irregular menses with bouts of amenorrhoea and occasional menorrhagia. No response to hormone replacement therapy. Hormone assays normal.

Curettage was carried out—very little endometrium obtained. The cervix was noted to be small and fibrous.

Laparotomy—showed both ovaries to be the seat of early cirrhotico-cystic change. No ovulation. Both ovaries wedge resected and everted. Routine Gilliam suspension carried out.

(3) *A Case of Cystic Ovarian Atrophy*

Mrs. B. (Fig. 9). Aged 30 years. Menarche at 13.

Complains of infertility of 5½ years duration, accompanied by scanty infrequent menstruation. Periods of amenorrhoea up to six months in duration. No improvement with hormone therapy. Ketosteroid levels—normal. Gonadotrophins—normal.

Laparotomy—showed an atrophic uterus with cystic atrophy of both ovaries. No ovulation. Wedge resection and eversion of both ovaries carried out. Routine Gilliam suspension carried out.

Summary

I might summarize the main points of this communication as follows:

(1) Since 1937 I have not changed my initial beliefs with regard to the major factor of the association of bilateral polycystic ovaries with the clinical aspect of the syndrome described by Stein and Leventhal, but would suggest that the basic gonadotrophic dysfunction concerned might also result in certain other changes in the ovaries (cirrhosis, cirrhotico-cystic change, cystic and cirrhotic atrophy), which are also associated with the clinical symptoms identical with those of the Stein-Leventhal syndrome, and which call for the same surgical treatment—although with the expectancy of less favourable results.

(2) The aetiology of this syndrome and the ovarian changes associated with it remain in doubt. I here suggest my own view upon this, which differs to some extent from those already

propounded, and upon which I base the operative technique in my treatment.

(3) Pathologically I recognize 3 main types of ovarian changes in conjunction with the clinical aspects of this syndrome: (I) The polycystic ovaries, which constitute about 80 per cent of my cases. (II) The cirrhotico-cystic and diffuse cirrhotic ovaries, and (III) cystic and cirrhotic atrophy of the ovaries. These may result from gonadotrophic dysfunction initiated *de novo*, or possibly may result by slow retrogressive change from the former type.

(4) The rationale of ovarian eversion combined with Gilliam suspension is again described. All forms of medical and hormonal treatment must first be tried. It is however unwise to unduly prolong medical treatment where there is evidence of no success and where examination discloses the presence of the uterine, endometrial and ovarian changes described.

(5) Approximately 80 per cent of my cases conform clinically and pathologically to the Stein-Leventhal syndrome. I feel nevertheless, that these may be regarded as forming the major part of a large clinical hormonal syndrome caused and initiated by the same type of gonadotrophic dysfunction, and manifested only by the degree to which this dysfunction is operative in the particular individual.

I wish to record my appreciation and thanks for the photographs taken during operation, and the film showing the operative technique, to the Staff of the Department of Medical Illustration under the direction of Dr. R. Ollerenshaw, and for the histological work and preparation of photomicrographs to the Department of Pathology at Saint Mary's Hospitals, under the direction of Dr. F. A. Langley, and also to my Chief Assistant, Dr. D. C. Aird, who has helped me to collect and re-investigate the clinical material.

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STRUCTURE, ORIGIN AND HISTOLOGICAL RELATIONS OF DYSGERMINOMA

BY

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OVARIAN dysgerminoma is in this country one of the rarest, and in all one of the most mysterious, of the primary ovarian tumours. The present article records a detailed study by multiple section of an individual case; and this is supplemented by a similar study of a testicular tumour with features both of seminoma and "embryonal carcinoma" of adeno-papillary type. The latter is put in to aid the discussion of comparisons that have of recent years been made (e.g., by Teilum, 1943, 1946) between certain ovarian and testicular tumours.

MATERIALS AND METHODS

The material consisted of the two tumours mentioned, and both were studied by serial section (cut mostly at 8–10μ) of substantial parts but not of all: details are conveniently deferred to the text. Of the parts so studied, every twelfth section was mounted and stained by Harris's haematoxylin and eosin: the intervening sections were kept in their correct order, and mounted and stained where appropriate by this or other stains. These are conveniently indicated in text or captions; but one—referred to as a "modified Wilder"—must be described here, since it is unpublished. Its aim is to demonstrate cells, reticulum fibrils, and their relations intelligibly in the same section. The sections are brought to water, and oxidized for 5 minutes in 1 per cent potassium permanganate. They are then rinsed and reduced till colourless or a uniform pale grey in 1 per cent aqueous gallic acid. This is the essential step, and it is important that the next stages up to impregnation be expeditious, as otherwise the gallates in the section (which throw down a uniform mild silver deposit) get washed out. The section is rinsed briefly (1 dip) in tap water, placed in 1 per cent aqueous uranyl nitrate for 30 seconds, rinsed briefly in tap water and two changes of distilled water (1 dip each), and then placed in Foot's ammoniacal silver for 2 minutes. The section is then rinsed in distilled water (6 dips) and reduced in 1 per cent neutral formalin. The subsequent stages—gold, oxalic acid, thiosulphate, dehydration, etc.—are routine, and need not be detailed. This method should produce black reticulum fibrils, with well-toned brownish cells in between: the photographic prominence of the latter may be varied by suitable choice of filter. All material was fixed in 10 per cent formalin and embedded in paraffin, except for a single frozen block made from the first tumour.

FINDINGS

Case 1. The patient, a single woman aged 25, had had abdominal pain and loss of weight for 3 months. The pain became severe on the day of operation, when she was admitted as a case of acute appendicitis. Her periods had been regular, and she had had no children or abortions. At laparotomy (29th October, 1954—Mr. L. D. C. Austin) a unilateral solid ovarian tumour, with its attached tube, was removed. Recovery was uneventful. The patient married 1 year after operation, and subsequently had 2 children. She was alive and well in June, 1958, over 3½ years after operation.

The excised object (which was sent to me in 1957 from Colombo by Professor G. H. Cooray)

consisted of a lemon-shaped, apparently right-sided ovarian tumour ($9\times7\times6\frac{1}{2}$ cm.), with its attached tube. It was rather knobbly, the knobs varying from $\frac{1}{2}$ to 4 cm. in width. It had assumed the faint pale pink colour sometimes found in objects kept for long in formalin. The cut surface was of similar colour, uniformly solid, with a suggestion of friability (though now made firm by fixation) and some unobtrusive fibrous septa. There was no obvious gross ovarian remnant, though several were later found on microscopy. Figure 1 shows the gross appearance of the object, which has been bisected down its long axis. The upper right half shows the attached tube along its right-hand border. The principal ovarian remnant is marked with an "x": it extended down the visible limb-like protuberance on which this is written, grew smaller in cross-section, and eventually faded out. The lower half is so arranged that its upper edge corresponds to the adjacent one in the other: the tumour has (so to speak) been opened here like a book. The portions enclosed in black lines (which included the whole thickness of the two pieces, and probably amounted in all to about half the total tumour volume) were cut serially. About 9,000 sections in all were cut, but only somewhat over a thousand mounted.

Figures 2–4 show successive cross-sections—moving leftwards and downwards—through the main ovarian remnant "x" of Figure 1. This remnant is seen in the obvious bulbous projections to the right of Figures 2 and 3; and below, on the right and not projecting (smaller and about to disappear) in Figure 4. In Figure 2 the cortical part of this remnant lies mainly along the lower border of the projection, the rest of this being broad ligament fibro-muscular tissue and vessels: it is seen as a dark band. In Figure 3 this band has spread both ways—over and round the crown of the projection and down into the tumour capsule. Subsequently the projection retreated to give a flat dark surface band of cortex, surmounting a pale area of medulla; and this is seen in Figure 4 below the main surface infolding, where the ovarian remnant is still present but is attenuating. In Figure 5, from the opposite tumour half (the lower enclosed portion in Figure 1, specifically), another ovarian remnant is seen below and to the left, with a peripheral dark rim of cortex frayed at its lower border: this was the second largest example found. The nodular character of the growth is very evident in this figure.

As may be seen in Figures 2–5 the dark ovarian cortical rims continue more or less tangentially into the dark nodules of tumour growth, whilst the subjacent pale medullary portions continue between these nodules as pale cell-poor connective tissue septa with prominent thin-walled vessels. The relation is best seen in Figure 2, but is visible in all. These septa ramified through the tumour to form an incomplete spongework (cf. Figure 4, especially): some had been encroached on by tumour growth, so that isolated pale islands (of similar structure to these septa) were found completely surrounded by tumour. This topography suggests that the tumour is essentially a nodular expansion of the cortex in basic architecture; and this was consonant with the finding within its substance of primordial and early ripening (Fig. 8) and late ripening (Figs. 3 and 4) follicles. These were found in all quarters of the tumour; but the former were commonest near the main cortical remnant of Figures 2–4.

At one point in the progress down this remnant (the "x" of Figure 1), shortly before the site of Figure 4, a quite separate nodule of tumour appeared within the dark cortical rim. This started superficially, ran for about 3 mm. within the rim (continually expanding in cross-section), and finally united with the main mass of tumour. A low-power cross-section of this "tumour-neck"—about $\frac{1}{2}$ mm. from its beginning at the surface—is seen in Figure 6 as a fusiform expansion of the ovarian cortex on the right; the main tumour mass is seen to the left, with some pale ovarian medulla in between. In this piece of cortex were found the only structures that could be interpreted as intermediate (and therefore transitional) between tumour and normal ovarian elements: they are seen in Figure 7, which is from a section close to that of Figure 6. There are seen, above and to the right, two quite typical primordial follicles; throughout, ovarian stroma, with a few scattered tumour cells therein; and—at two points, near the bottom left and middle right—two equivocal structures which seem like a

compromise between tumour cells and primordial follicles. Unfortunately, the certainty of this assessment is much impaired by the poor preservation of detail, due mainly to long residence in fixative.

The tumour pattern itself was quite typical, and consisted of nests and cords of rather large polygonal cells, without further differentiation of pattern at any point. The detailed impression varied with whether the tumour cells had shrunk away from their connective tissue septa, as in Figure 9—which produces a slight stylization of pattern; or whether the shrinkage process had instead separated cell border and nucleus, as in Figures 8 and 12—which merely produces a large pale cell. The deeper parts of the tumour were often poorly fixed and showed much cellular dissociation: adherence of some of these cells to the connective tissue septa produced a pseudo-papillary impression which was clearly artefactual. Connective tissue septa ran through the tumour in a centrifugal tree-like pattern, to end usually in a broad or narrow capsule. Both these and the tumour parenchyma showed a scattered lymphocytic infiltration, with occasional aggregations but no lymphadenoid foci: a few Langhans-type giant cells were seen.

Relations at the surface varied. Mostly the tumour tissue was bounded by a fibrous connective tissue capsule, broad or narrow, which might show a scattered infiltration by tumour cells (Fig. 8): the broader parts of this often showed primordial or early ripening follicles. In several places this capsule attenuated down to one or two broad collagen fibres. In a few places further attenuation occurred, and the tumour tissue here bulged outwards into little tufts with smooth outer surfaces. Two such tufts are seen at very low power in Figure 5—one as a low bulge just below the mouth of the main surface pit entering from the left, and the other as the polypoid protrusion at the top. The first of these tufts is shown at somewhat higher power in Figure 10: a rough general resemblance to embryonic ovary of about 120 mm. will be noted. This resemblance extends to certain details. Part of the surface of this bulge is seen in Figure 12 at higher power: there are seen (from right to left) a layer of surface epithelium; an ill-defined layer of condensed, rather small cells; and irregular nests of large pale cells with scattered lymphocytes. The general resemblance to embryonic ovary (Fig. 15) is evident, though in the latter (which is better fixed) the layering is more clear-cut; the point will be pressed in more detail in the discussion. A similar layering is seen in Figure 11—also from this bulge: in the condensed subsurface layer two germinal (or dysgerminal) cells can be seen pressing up against the surface epithelium. The resemblance extends to the pattern of the reticulum. Most of the surface showed a sub-epithelial basement membrane of more or less condensed reticulum fibrils, though this often retreated from the surface epithelium to surround a subsurface bay containing one or two tumour cells. In some areas (as in Figure 13, which corresponds to Figure 12) this membrane became wholly interrupted; but the surface epithelium (resting directly on the layer of rather small cells shown) none the less remained straight. A reticulum impregnation of the second tuft mentioned is shown in Figure 14. In an ordinary preparation this lacked a distinct surface epithelium: the surface (which none the less remained straight) was covered by a thin layer of exudate containing a few isolated cells of uncertain status. The reticulum impregnation demonstrates conclusively the absence of any subsurface basement membrane. Figures 13 and 14 may be compared with the similar findings in Gruenwald's (1942) Figures 3–7 and 14: the reticulum impregnation of the ovary of Figure 15 was similar.

The tumour showed a number of surface projections of young vascular new connective tissue: Figure 6 shows one, adjacent to a surface infolding. At no point was there clear evidence that the tumour cells had broken through to the exterior (though it was not always easy to distinguish them from proliferating surface cells); nor could unequivocal lymphatic permeation be seen. Tumour cell mitoses were scanty. In frozen sections fine sudanophil droplets were seen, in variable amount, in the cells of the tumour. There was no doubly refractile lipoid. Some granules of glycogen (Best's carmine) could still be demonstrated patchily. The ovarian remnant showed primordial, ripening, and early atresing follicles: there were numerous corpora

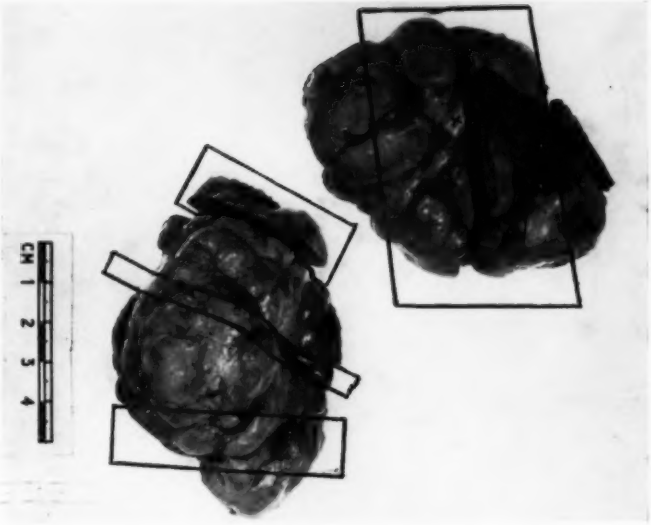

FIG. 1

Case 1. The gross specimen, bisected down its long axis, showing folded and knobbly surfaces. The half above and to the right shows the attached tube down the right hand border, with its fimbriated end below, and some folded broad ligament to its left: the cut part of this is beyond the tube and is invisible. In the centre is the main ovarian remnant, marked "X". In both halves the portions enclosed in black lines were cut serially.

FIG. 2

Section across proximal end of main ovarian remnant ("X") and adjacent tumour. The rounded protuberance to the right above is mainly broad ligament, but shows a dark band of ovarian cortex along its lower border. To the left of the broad ligament is medulla, which continues between the dark tumour masses as pale septa. H. and E. $\times 2\frac{1}{2}$.

FIG. 3

The same, a little lower. The projecting knob is now entirely ovary, the cortex of which shows as a dark periphery and also extends downwards into the tumour capsule. Medulla as last. Two ovoid late ripening follicles can be seen in the tumour substance near the bottom. H. and E. $\times 2\frac{1}{2}$.

H. and E. ×2½.

FIG. 4

The same, lower still. The ovarian remnant is seen to the right a third of the way up: it is now much flattened and reduced in size, and it shortly faded out. Its dark cortex continues above and below into dark tumour masses, and the pale medulla between them. A late ripening follicle is seen in the tumour substance near the top, and a somewhat smaller one in a septum below and to the left. H. and E. ×2½.

FIG. 5

General view of other half of tumour, showing very nodular structure, pale internodular zones, and ovarian remnant three-quarters of the way down to the left. The narrow dark band of cortex of this last continues into the dark tumour masses, and the pale subjacent medulla between them. H. and E. ×2½.

FIG. 6

Low-power of view of part of cortex of ovarian remnant at a point slightly above the plane of Figure 4. Its fusiform expansion (to the right of centre) is a nodule of tumour (separate from the main body) surrounded by ovarian cortical stroma. This ended blindly proximally (i.e., towards Figure 3). Distally it fused—after a course of 3 mm.—with the main dark tumour mass to the left, here separated by medulla. H. and E. ×10.

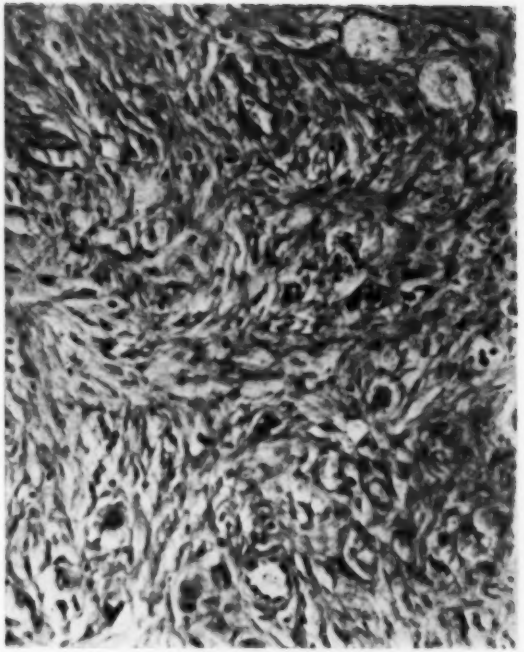

FIG. 7

Ovarian stroma at the edge of cortical nodule of Figure 6, near its proximal end, showing two primordial follicles above and to right, a few tumour cells scattered in ovarian stroma, and two structures of equivocal and intermediate appearance between the two. H. and E. ×225.

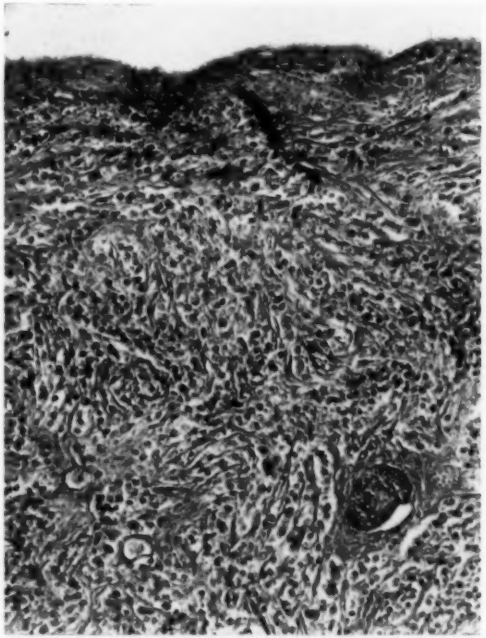

FIG. 8

Part of tumour from point corresponding to lower part of Figure 2, showing cords of pale tumour cells, with two included primordial follicles below to left and two ripening ones to right (somewhat tangentially cut), and capsule infiltrated by tumour cells above. H. and E. ×100.

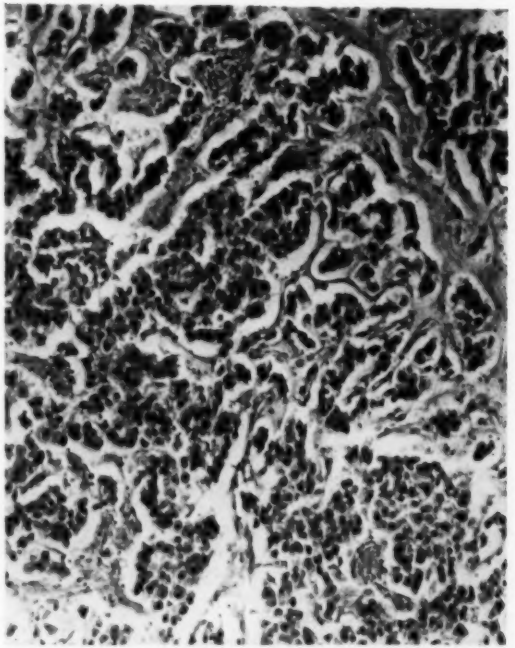

FIG. 9

Part of tumour pattern from point corresponding to the upper edge of Figure 3, showing agglutinated nests and cords of large tumour cells which have shrunk away from their intervening connective tissue septa and present sharp margins to the spaces created. H. and E. ×115.

FIG. 10

Low-power view of projecting knob visible in Fig. 5 below mouth of main infolding on left. It shows a rough general resemblance to embryonic ovary, with egg-balls and smooth outer surface, notwithstanding that the tumour tissue is through its capsule. H. and E. ×45.

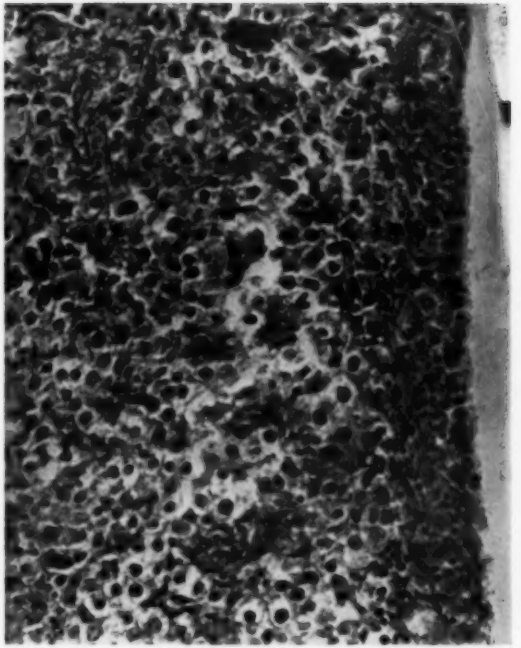

FIG. 11

Part of upper surface of nodule of Figure 10, showing nests of large pale tumour cells to left, narrow condensed subsurface zone, and surface epithelium to right. H. and E. ×190.

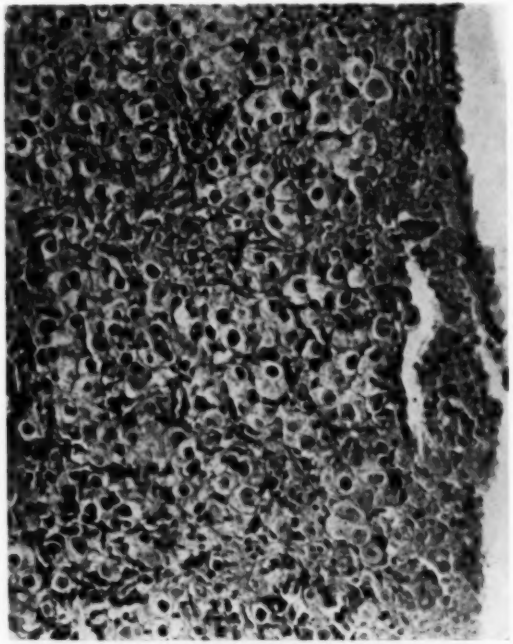

FIG 12

Part of left-hand surface of nodule of Figure 10, showing nests of large pale tumour cells, narrow subsurface zone of smaller cells, and surface epithelium. The split to the right is artefact. H. and E. ×200.

FIG. 13

Reticulum impregnation of similar region to last, showing straight epithelial surface despite absence of continuous subjacent basement membrane. Modified Wilder. ×160.

FIG 14

Reticulum impregnation of surface region of projecting knob at upper end of Figure 5: note straight surface to right, despite total absence of a subsurface basement membrane. Modified Wilder. ×155.

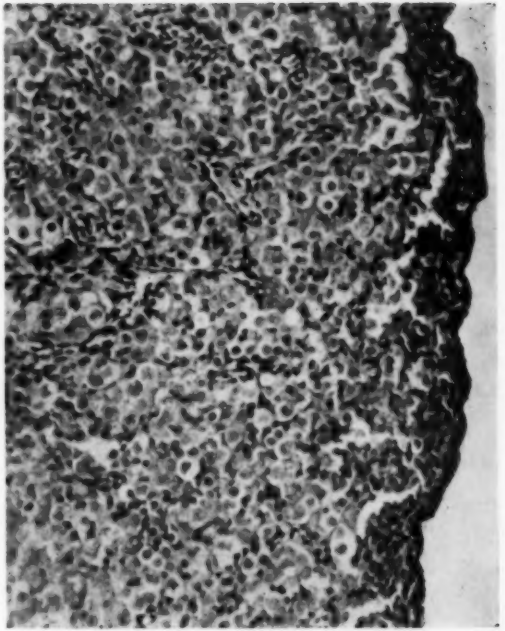

FIG. 15

Surface region of ovary of 120 mm. foetus, showing surface epithelium to right, subsurface zone of condensed small cells, and nests of pale germ cells to left. Compare with Figures 11 and 12. H. and E. ×200.

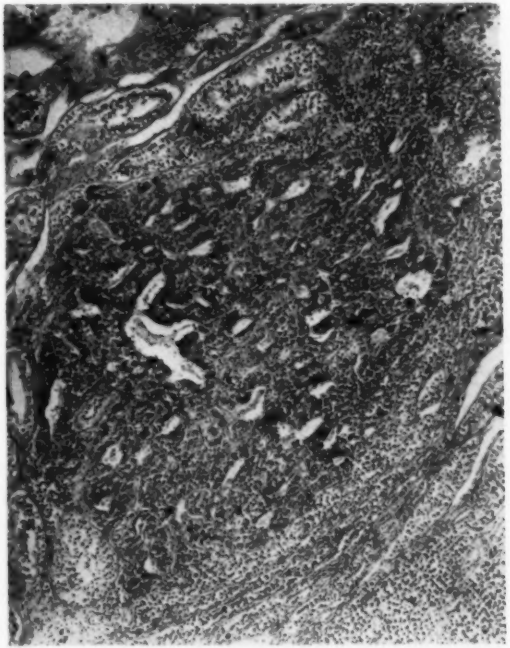

FIG. 16

Case 2. Tumour of testis, showing nodule of embryonal adenocarcinoma in centre, with seminoma to right and below, and seminiferous tubules to left and above. H. and E. ×55.

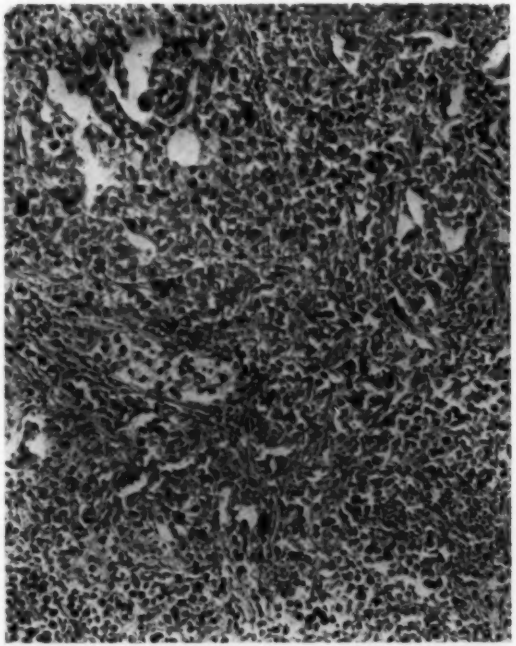

FIG. 17

The same. Junction of the two patterns, showing gradual transition from embryonal carcinoma above to seminoma below. H. and E. ×115.

fibrosa, and a single corpus albicans was seen at the beginning of a tumour septum, where it joined the medulla of an ovarian remnant.

Case 2. The patient, a man of 25, had noticed a progressive painless swelling of the right testis for 4 months, and some recent loss of weight. A right orchidectomy (23rd February, 1950—Mr. Cameron MacLeod) was done at the Hampstead General Hospital, and the patient was shortly referred to University College Hospital for radiotherapy. After a course of this he remained well for about 18 months: then he began to lose weight, and died on 3rd March, 1952, with multiple metastases to lungs and brain.

The excised object consisted of an enlarged right testis (7×4×5 cm.) and cord. The upper half of the testis was occupied by nodular tumour masses, partly firm and partly soft, partly greyish-white and partly haemorrhagic. From this tumour 8 blocks were made and about 2,200 sections—mostly serials—were cut. It was not possible, however, to reduce the whole tumour to serial sections—partly because the borrowed three original routine blocks could not be so cut, and partly because one block was lost after only 100 sections had been cut off. It is estimated that at least half the tumour was cut serially; and the rest of it was well sampled, inasmuch as no part of it remained unblocked.

The tumour had a conspicuously nodular structure, with two types of histological pattern (Figs. 16, 17)—namely, typical seminoma and typical "embryonal carcinoma" of adeno-papillary type. These will not be described in detail, as the present article is only concerned with the relations between them: in both, the patterns corresponded to the account of Dixon and Moore (1953), to which the reader may be referred. Both patterns showed glycogen (Best's carmine), patchily preserved; no frozen blocks were made. The seminoma differed in structure (or structural range) from that of Case 1 mainly in its much lower complement of connective tissue. It showed several areas of intra-tubular growth, notably at the margins of the seminoma nodules: the seminiferous tubules otherwise varied from normal to extreme degrees of maturation arrest. The embryonal carcinoma showed adenoid, adeno-papillary, and solid areas: some of the latter were cribriform, with adenoid spaces, and a few were purely solid, and so approximated to seminoma in appearance; but in no area (save one shortly to be described) did it grade into unquestioned seminoma. The adeno-papillary parts showed some prominent intra-papillary blood vessels, producing the perithelial pseudo-glomerular appearance noted by Teilum (1943). This tumour half showed gross intra-vascular permeation, both within its substance and at the hilar (rete) region; and many parts showed extensive areas of haemorrhage, presumably consequent on vascular erosion. No overtly teratoid features and no tissue patterns other than those mentioned (as, e.g., nodules of cartilage) were found. Relations between the two patterns varied. At some points (where the junction between the two patterns was abrupt) the embryonal carcinoma formed a protrusive bay into the seminoma, suggesting that it had erupted into it. In Figure 16 the junction was also abrupt, but relations were different. The figure shows a mainly adenoid nodule of embryonal carcinoma, sectioned near its middle. The nodule was cut serially from end to end, which established that it was entirely separate from any other tumour nodule of the same pattern. It was not associated with any marked effusion of blood, though its lumina contained some red cells. It was surrounded, to the extent of from two-thirds to three-quarters of its circumference, by a more or less narrow seam of seminoma, but in places (as in Figure 16 below and to the left) it abutted directly on seminiferous tubule basement membrane. A few seminiferous tubules were found within the nodule. There was nothing suggesting a significant transition either to these tubules or to seminoma. Figure 17 shows the only area found in the tumour where a completely smooth transition between the two patterns occurred. Above is seen embryonal carcinoma, which is here mainly solid but higher up became similar to Figure 16. Below is typical seminoma; and the change-over from one pattern to the other is so smooth that neither here nor in adjacent sections could one say certainly where one ended and the other began. A reticulum impregnation of a corresponding region showed no particular heaping up at the site of junction: in general the reticulum was relatively more

subdivided in seminomatous areas. The tumour zones just described had (very roughly) the form of an hour-glass, inasmuch as they were connected by a narrow neck: Figure 17 was taken from this neck.

Discussion

The only feature here worth mentioning of the detailed structure of these tumours is the slight agglutinative tendency of their cells. This is able to show itself when these shrink away from their connective tissue septa, as in Figure 9. The result may be sharp palisaded margins to the cellular groups (present at some point in both the tumours described) or slight stylization of pattern. These characters are less marked than with mature granulosa cell tumours, but have been known to cause confusion—a noteworthy instance being in von Werdt's (1914) original 6 cases (the first reported under this title), of which the first and last were clearly dysgerminomas.

General architecture needs more discussion. It seems clear (if my Case 1 is typical) that the tumour is essentially cortical and is made up of multiple nodular expansions of the cortex. In this it resembles some secondary tumours—notably the Krukenberg; but it lacks the reactive stromal proliferation, and also the medullary oedema (which is usually attributed to plugging of the hilar lymphatics by growth). This view of the tumour hinges on two main points—firstly, on the presence of primordial and early ripening follicles throughout its substance; and, secondly, on the topographical continuity of the tumour masses with the margins of the cortical remnants and of their intervening septa with the medulla. Regarding the first point, similar findings have been recorded by von Werdt (1914, Case 1), L'Esperance (1928, Case 1), Babes (1929), Hain (1949) and Forster (1953, Case 7). The included follicles here serve only inferentially as topographical markers: there is no suggestion of any transition between them and the cells of the tumour. The early stages (as in Figure 8) have the most value here. Late ripening follicles, though commoner in the cortex, may also be found in the medulla; an example, deep in a tumour septum, is seen a quarter of the way down Figure 4. Regarding the second point, it might seem that as the tumour had evidently in places encroached on the medulla and its supposed septal derivatives (detached islands of which were found wholly surrounded by tumour tissue), and as it had certainly encroached in many places on the cortex (to the extent of replacing all or part of it), no inference could be made as to that in which it actually began. This objection seems reasonable only in the abstract. Medullary tumours are a definite architectural entity, and fall into two distinct groups. One, comprising granulosa cell tumours and arrhenoblastoma, appears to begin in the hilar cortical tongue and to grow backwards into the medulla (Hughesdon, 1958). The other (which is clearly of more obscure origin) consists of the benign teratomas: such few small dermoids as I have cut serially have been medullary, and the same is true of *struma ovarii* (Hughesdon, 1955). In either group the tumour tissue is separated from the encapsulating ovarian cortex by a layer of vascular cell-poor connective tissue. As typical cortical tumours one may take adenofibromas and cystadenomas, which (when small) may readily be seen to occupy local expansions of the cortex. As they grow, they push the medulla to one side, and stretch it round part of their periphery. The present case was similar, with the vital difference that its cortical sites of growth were multiple: the tumour, consisting of multiple local expansions of the cortex, encroached on the medulla from all directions, and so stretched and distorted it into an interrupted spongework. The obvious inference is that the tumour began in multiple foci throughout the cortex, and (within this) the most likely candidate for the cell of origin is the oöcyte.

In an earlier article (Hughesdon, 1958), a principle was developed for inferring the histogenesis of an adequately studied ovarian tumour, based (as formulated) on the deduction from the topographical form of the tumour that it had grown away from—rather than towards—any site found of histological blending with ovarian tissue. The qualifying stipulation was made that not all tumours will yield definite results; but the formulation was slightly defective,

inasmuch as it did not clearly distinguish two types of relative growth—growth of the tumour tissue relative to the ovarian tissue as a whole, and growth relative to that part which immediately bounds it (and to which alone significant histological transitions can occur). This defect is easily remedied by a brief restatement. If a tumour expands equally in all directions so as to acquire the form of an orange, then its tissue will (on an average) have moved away from the host ovarian tissue at its immediate periphery to an equal extent all round; the topography does not single out any part of this periphery as the site of origin, and so cannot fortify the implications of any histological blending that may be found. Such purely expansile growth will however usually move the tumour away from the ovarian tissue on an average, in the simple sense that the centre of gravity of the tumour and of the ovary will move apart; and it is possible that some significance may be attached to the direction of this movement. If however (as is both more common and more important) the tumour grows unequally, so as to acquire, for example, the form of a pear (or have a body and neck), then clearly the centre of gravity of the tumour (and so the tumour tissue on an average) has moved farther away from the point of attachment of the stalk of the pear than from any other point of the periphery. The general direction of growth being then away from the stalk, any intimate blending of tumour and ovarian tissue there is established as primary and not secondary—that is, as histogenetically significant; this was the situation in Case 1 of the article cited. It is important to note that *relative* growth is the point at issue. It would be irrelevant to object (in the case of a pear-shaped tumour) that the body might form first and the neck second; whatever the details, the bulk of tumour tissue has moved *relatively* to its surroundings most markedly away from the neck region. (But it may reasonably be added that the compact convergent form of a pear-neck would be unlikely to result with a connexion established secondarily by invasion.) Such an inference will be strengthened if the neck is relatively longer than that of a pear, and still more if it is bent relative to the main body of the tumour—implying in addition that the expansion of the latter is a later development. This was the situation in Case 2 of the article cited, and also in the present Case 1. Figure 6 shows the tumour neck running roughly parallel to the rest, and Figure 7 the transitional appearances found near its beginning. The finding does not carry much weight, however, partly because the neck was so short relatively to the size of the tumour, and partly because the rather poorly preserved appearances of Figure 7 are not very convincing. Similar structures—of appearance intermediate between primordial follicles and isolated tumour cells—have been described and figured by Babes (1929).

A second line of approach might rely on the comparison of the tumour with embryonic ovary, of about the 120 mm. stage, when the histology is dominated by masses of "egg-balls" (cf. my Figure 10). There can be little doubt both that there is some resemblance, and that the tumour does not resemble any other non-neoplastic structure. Cases are published in which it is uncertain which of the two entities one is dealing with: thus, Lindvall and Wahlgren's (1940) Case 3, presented as an ovotestis in which the ovarian part had retained a foetal structure, would do equally well for an immature testis with an early seminoma. Recently Bradbury and Burge (1958) have compared a similar immature gonad in a case of gonadal dysgenesis with these tumours. However, the force of any comparison which a general impression may suggest depends on the number and specificity of the points of correspondence. The points of correspondence between Figure 15 (the ovary of a 120 mm. embryo) and Figures 11–13 (an area where the tumour lacks any vestige of a capsule) are the zoning into surface epithelium, a narrow subsurface condensed zone of cells which tend to be rather small (more especially in Figures 12 and 13), and the deeper nests of large pale cells of apparent germinal type. With a reticulum impregnation a further point emerges in the lack of a continuous subsurface basement membrane in either, as shown in Figures 13 and 14. The reticulum impregnation of the ovary of Figure 15 showed a picture intermediate between Figures 13 and 14: comparable patterns

are seen in earlier gonads in the article and figures of Gruenwald (1942) already cited. Notwithstanding this, the tumour (like embryonic ovary) maintained a smooth outer surface. The remarkable ability of the unsupported surface epithelium to retain the proliferating germinal cells is attested by the patient's survival. There is also conveyed by this particular pattern some impression of an origin of the germ or tumour cells from the surface epithelium (cf. Fig. 11). Whether in fact this impression is correct or misleading is immaterial; it is enough that it occurs in both structures when there is no basement membrane, and so fortifies the comparison.

There is some scanty literary precedent for these surface relations. Glockner (1905, Case 24), writing at a time when the tumour was not a clearly recognized entity, described a right-sided ovarian "carcinoma"—soft, completely solid, and whitish-grey on section—in a girl of 20; she died from metastases 2 years after panhysterectomy. Sections of the tumour (not figured) showed large polygonal cells (17 μ in diameter, with 12 μ nuclei) arranged in nests and cords, with well developed connective tissue septa infiltrated with round cells and some "tubercles": the last were also found in the lateral pole of the left ovary. The tubes were patent, and there was no evidence of tuberculous peritonitis. A retrospective diagnosis of dysgerminoma here seems to me a virtual certainty, if one takes in conjunction the patient's youth, the gross and microscopic description of the tumour, and the pseudo-tubercle (well known in this tumour, and first shown by Schiller, 1934, to be habitually void of bacilli). In that case, the following comments of Glockner are of interest: "Surface epithelium, often preserved, shows frequent sinkings into the underlying connective tissue and often stands in intimate association (*Verbindung*) with collections of tumour cells lying near the surface . . . The tumour represents therefore a very cellular typical carcinoma, for whose origin from surface epithelium much appears to speak" (pp. 87–8). Peyron (1922) described and figured (Fig. 21) less clearly a similar relation of tumour cell cords to hilar surface infoldings.

The germinal nature of the essential cell of this tumour was deduced by McKay, Hertig, Adams and Danziger (1953) from the presence of a marked alkaline phosphatase reaction just beneath the cytoplasmic rim. They had previously used a similar finding for throwing the primordial germ cells into relief, and demonstrating their gradual migration from the hindgut. They suggest that the tumour reproduces the morphogenesis of the primitive gonad; but there seems to be no essential reason to postulate some primitive, undeveloped or primordial germ cell as its cell of origin. The simple and natural view (postulating the minimum that is either unverifiable or unprecedented) is that these tumours are analogous to, rather than homologous with, those in the male, in that they develop from the normal cells of the female germinal lineage—in effect, the ova of primordial follicles; and that the relatively primitive cell type (as well as the occasional quasi-embryonic surface pattern) is a reversion due to neoplasia. This accords with the preferential age incidence of the tumour in youth brought out in the reviews (von Szathmary, 1933; Mueller, Topkins and Lapp, 1950), which (except for the first decade) corresponds well enough with the steep falling off in the total number of primordial follicles in both ovaries with advancing years (Block, 1952); the exception may reflect the lack of stimulation of follicles and oöcytes at this period. It accords also with the frequent radio-sensitivity of the tumours (Santesson, 1947). The only objection to this view is the total failure of the supposed constituent germ cells to mature to the later stages in the tumours of either sex; for most tumour types contain examples or possess homologues with areas of full—and sometimes excessive—differentiation. One possible explanation—the absence of attendant granulosal or Sertoli cells—would seem ruled out by the recently described "gonadoblastoma" of Scully (Scully, 1953; Morris and Scully, 1958). In this curious entity isolated germinal cells are figured as dotted about in nests and trabeculae of granulosa-type cells without any apparent sign of further maturation. Apart from this, the theory outlined covers the facts, and has perhaps been generally overlooked or disregarded because of its obviousness.

The three traditional views of the tumour's origin are more recondite. It was first identified as an entity by Chenot (1911); and it is a historical accident (though an understandable one) that the testicular tumour was identified first (Chevassu, 1906). An obvious inference was that the ovarian tumour arose from some part of the organ to be regarded as quasi-testicular; and this view (though not that of Chenot) has mostly been favoured by French writers, who have continued to use the term "ovarian seminoma". This hypothesis is verifiable, in that a small tumour might be traced either to some recognizably seminiferous structure or to some region of the ovary held on other grounds to be homologous with testis; so far as I am aware, neither has been done. The distribution of my own tumour as multiple cortical nodules does not favour the idea, as it is usual to attribute testicular homology to some part of the medulla or hilus. Also against it is a case of Polano, re-described by Meyer (1931a, I), of a patient with an ovotestis on one side and a dysgerminoma on the other. In the ovotestis (not apparently cut serially) a small early focus of dysgerminoma was found in the deeper part of the ovary. Meyer thought this to be a second primary rather than a metastasis; and (if he was right) it clearly could not have arisen in any testicular rudiment or homologue, for here this would have been converted into testis.

Meyer's own theory (which is similar to that of Chenot) of an origin from "indifferent germ cells" (Meyer, 1918, 1925, 1931b) must surely be one of the oddest ever to achieve textbook dissemination and general currency. It has several possible meanings, but only two seem potentially relevant—namely, that the tumour is derived from persistent rests of the earliest recognizable germ cells in the gonads (these being similar in the two sexes and like the cells of the tumour); and, secondly, that it derives from persistent rests of the indifferent phase of the gonad (such tissue being "germinal" only in the quite different sense of germinating gonadal tissue). The first interpretation seems to be favoured by Morris and Scully (1958), and the second by Ewing (1940) and Novak (1948). It is unnecessary to discuss the authenticity or plausibility of either view, for both are quite unverifiable: the very indifference of the postulated tissue of origin would render its identification in an ovarian remnant attached to a tumour quite impossible. This does not prove the view false—merely that there can be no respectable reason for believing it true. All the indirect evidence adduced by Meyer—the preference of the tumour for intersexes, for malformed or misplaced gonads, and its occurrence in either sex—applies with equal force to the tubular adenoma, for which he had a different explanation.

A third view was adumbrated by Pick (1904, 1905): in describing and discussing various odd ovarian tumours, he implied that what is now called dysgerminoma and was then known more vaguely by descriptive terms (such as "alveolar sarcoma") was essentially a chorion-epithelioma consisting of Langhans' cells only, the occasional symplasmic giant cell being a rudimentary attempt to form syncytium. As a piece of pure histology, the imputed cellular likeness seems neither great enough to establish the idea nor slight enough to refute it; but some weight has since been lent to it by the many cases published (Hain, 1949; Morris and Scully, 1958) associated with a positive pregnancy test. More recently a modified and elaborated version of this theory has been put forward by Teilum (1943, 1946), according to whom there exists a family of three homologous tumours—occurring alike in testis and ovary—consisting of seminoma or dysgerminoma, chorion-epithelioma, and certain tumours of adenopapillary structure. These last are usually called "embryonal adenocarcinoma" in the testis: in the ovary they have been mostly described under either the label "mesonephroma" or some other designed to elucidate it (Teilum's term being "mesoblastoma"). These two adenopapillary tumours are said by Teilum to be homologous and to be intermediate between the other two. It is difficult to attach a clear meaning to this in the morphological sense —and none other is offered; but the important point is undoubtedly the weaker one that the three tumours are related and form a family. This poses different problems of fact in testis and ovary.

It is not proposed to discuss chorion-epithelioma of the testis, for which the reader

may be referred to Dixon and Moore (1953). My Case 2 affords evidence of a histogenetic connexion between seminoma and embryonal adenocarcinoma on two counts. The first is that the nodule shown in Figure 16 was cut serially and found to be quite separate from the rest, being largely surrounded by seminoma; the simplest interpretation would be that it developed *in situ* from this. A local vascular metastasis seems unlikely in the absence of extravasation. The second is the gradualness of the transition between the two patterns shown in Figure 17, taken in conjunction with the hour-glass form described of the zones connected—a form which suggests that they have been pulling apart rather than growing together (i.e., one invading the other). It is an open question whether these adenopapillary tumours of the testis are always teratomatous: it is certain that they can occur in conjunction with teratoid elements and may be associated with a positive pregnancy test. No structure other than seminoma and embryonal adenocarcinoma was found in my case; and, though it was not all cut serially, a great deal was.

Much of the early literature of ovarian chorion-epithelioma (reviewed by Forgue and Massabuau, 1907) is pre-photographic and difficult to evaluate retrospectively. Moreover, there is a major difficulty of principle in that, whilst undoubted uterine or gestational chorion-epithelioma may be highly atypical histologically, it would be difficult to accept as authentic an ovarian case without typical areas—that is, with nests of Langhans' cells more or less subdivided and surrounded by typical syncytium. Recent accounts have been given by Marrubini (1949) and Neigus (1955), each of whom reports a case associated with apparent dysgerminoma of the same ovary: in neither of these was there evidence of a connexion between the two structures. More recently, however, Talas, Jiratko and Krejci (1957) have reported a tumour showing both types of structure, with transitions between the two. A slight doubt attaches to the identification of the figured nests of clear cells as dysgerminoma; but otherwise the account seems convincing and supports Teilum's view. Primary non-gestational chorion-epithelioma of the ovary is, however, very rare: of far more interest is Teilum's suggestion that certain malignant adenopapillary ovarian tumours are homologous with embryonal adenocarcinoma of the testis and related to dysgerminoma. Two possible sorts of evidence might be produced for this. Firstly, such tumours might on occasion be associated with a positive pregnancy test: a single example of this has been reported (Santesson and Marrubini, 1957, Case 9). Secondly, adenopapillary tumours might be found associated with dysgerminoma, preferably with transitions between the two structures: it is clearly essential that the autolytic dissociation noted be not misidentified as truly adeno-papillary. Possible cases of this association may now be enumerated. Neumann (1925, Case 4) described a tumour combining the structures of a cystadenoma, dysgerminoma and a theco-granulosal tumour: the first was thought to be histogenetically related to the second. Gentil (1935, Case 12) described as an ovarian seminoma a partly solid, partly adenoid, rather clear-celled growth in a girl of 4¼. The two patterns showed transitions, but the identification of the solid part as "seminoma" seems questionable on the illustrations, though some weight must be given to the patient's age. Schiller (1939, Case 10) described a tumour showing dysgerminoma, adenopapillary and divers teratoid structures, whose histological interrelation is not defined: it seems more probable that the second was related to the third rather than the first. Kazancigil, Laqueur and Ladewig (1940, Case 1) described a tumour containing dysgerminoma, microfolliculoid granulosal, and adenopapillary elements. The relation of the first and third of these is unclear; the combination of the first and second would appear to place the tumour in the category of Scully's gonadoblastoma. Novak (1944, Case 34), annotating the first 50 specimens of the American ovarian tumour registry, reported an anaplastic carcinoma with papillary areas which some members of the panel considered to be a dysgerminoma; but the details given are necessarily meagre. Santesson (1947) mentions 7 tumours showing "different combinations of both adenopapilliferous, choriomatous, teratoid and dysgerminoma structures" amongst 33 "gonocytomas", but does not give details.

Hedberg (1955, Case 6) described a dysgerminoma in which "there was, in some areas, diffuse transitions to vegetations of adenomatous and papillary growth from the typical structure of dysgerminoma" (p. 241). It is a pity that this significant finding was not illustrated. Santesson and Marrubini (1957), amongst 17 adenopapillary tumours designated as "mesoblastoma" of the ovary, mention 5 as containing elements of dysgerminoma; but of these, in one (the most marked example) the dysgerminoma tissue was separated from the rest by a fibrous tissue capsule, whilst in the other 4 tumours "there were only a few scattered areas suggestive of dysgerminoma" (p. 413). It seems clear that the factual evidence for Teilum's views is still rather slight, but also that the field is a promising one for further study.

One may ask how a germ cell tumour could give rise to an adenopapillary tumour, or how the second (usually regarded as of surface origin in the ovary) could be related to the first. In the absence of clearer data, no certain answer can be given; but my Figures 11–13 show an intimate relation of dysgerminoma to ovarian surface epithelium, such as might suggest an origin there—much as (in a different way) occurs with adenopapillary tumours. Whatever the force of these respective suggestions, it seems at least possible that the epithelium of the second may retain a similar relation to the cells of the first as does surface epithelium, if both tumour types occur together (i.e., that one has here to do with an unusual form of mixed tumour). As to the temporal relation of dysgerminoma to the several other types of tumour mentioned, the views of Ewing (1940) are fairly well known: he wrote "that the cell of origin of the ovarian seminoma, as of the testicular tumour, belongs in the sex-cell series and that the tumours represent one-sided developments of a teratoma. In the testis the association with teratoma is very frequent." This formulation is highly ambiguous; but it has usually been taken to imply that first a teratoid tumour develops, and that subsequently a dysgerminoma or seminoma develops as a derivative of this. This view has been criticized, and may (I think) with advantage be put in reverse—to result in a developmental scheme similar to that of Santesson and Marrubini (1957). If dysgerminoma and seminoma consist of masses of proliferating cells of the germinal lineage, and, if these have either not lost or have regained the diploid state, then may they not on occasion acquire the same determinations as the similarly diploid mass of fertilized germ cells of the early ovum? The first three properties they might be expected to acquire as result are, on this analogy, an ability to erode and invade blood vessels (cf. my Case 2), an ability to produce chorionic gonadotrophin, and an ability to imitate early chorionic histological patterns. These acquisitions need not exactly correlate or be present in equal degree: thus the production of a positive pregnancy test by a minority of pure dysgerminoma is on all fours with the ability of some testicular purely adenopapillary tumours to erode vessels. Further developments may be expected to include more overtly teratoid tissues, so that the fact that some "embryonal adenocarcinomas" (a useful term, in that its uncertain meaning reflects the uncertain status of the tumour) are pure and some are associated with nodules of cartilage and other heteroplastic features is not so surprising.

Summary

(1) A dysgerminoma studied by multiple sectioning is described. This showed that architecturally the tumour occupied a nodular expansion of the ovarian cortex, because of (*a*) the marginal relation of the tumour nodules to the surviving cortical remnants, and of their internodular septa to the surviving medulla, and (*b*) the presence within the tumour substance of primordial and early ripening follicles. At one point in the cortex of the principal ovarian remnant a tangentially protrusive outpost or neck of tumour tissue appeared to be bordered by structures intermediate in form between primordial follicles and tumour cells, but poor preservation made interpretation difficult. At certain parts of the surface (where a continuous subsurface basement membrane was lacking) the tumour reproduced the pattern of an embryonic ovary (corresponding to a crown-rump length of 120 mm.), in that the

tumour cells blended (*via* a condensed subsurface layer) directly with a straight epithelial surface.

(2) A testicular tumour studied by multiple section is also described. It showed the two patterns of seminoma and so-called "embryonal adenocarcinoma". There were several zones where the second had clearly broken into the first. In addition, at one point an isolated nodule of adenocarcinoma was found largely surrounded by seminoma; and, at another, a zone of smooth transition from one pattern to the other was found at the site of a relatively narrow neck connecting two broad zones of opposite structure.

(3) In the light of the findings in Case 1 (for which some literary precedent is noted) it is concluded that the tumour arises from the oöcytes of the normal female germinal lineage, and reproduces the cytology and histology of more embryonic stages owing to neoplastic reversion. This view accords, not only with the tumour's histology, but also with its age incidence and radio-sensitivity. The theory of an origin from a testicular homologue does not accord with the architecture of the tumour; and Meyer's theory of an origin from indifferent germ cells is dismissed as ambiguous and unverifiable.

(4) The view of Pick, later extended by Teilum, relating the tumour to chorion-epithelioma and to certain adenopapillary tumours of ovary and testis is considered. It is suggested that Case 2 of this article favours the second of these postulated relations. A review of the literature suggests that in the ovary there is some evidence relating dysgerminoma to occasional tumours of the other two types, but this is as yet scanty.

I am much indebted to Professor G. H. Cooray for providing me with the first tumour, with data relating to the patient, and with permission to make use of them; and to Mr. A. Cameron MacLeod and Dr. A. E. Brewer for similar kindnesses in regard to the second case.

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SOCIAL AND BIOLOGICAL FACTORS IN INFANT MORTALITY* VARIATION OF MORTALITY WITH MOTHER'S AGE AND PARITY†

BY

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THIS paper deals with the relationship between a mother's age and the size of her family, on the one hand, and the chances of survival of her baby, on the other. The emphasis is on the way the relationship changes at different stages during the first two years of life, and particularly within the "perinatal" period—from the 28th week of pregnancy to the end of the first week of life. A further paper (Morrison, Heady and Morris, 1959) will deal more fully with deaths in the post-neonatal period and with the main causes of death at that stage—respiratory diseases, other infectious diseases and "accidents".

The data here examined relate to the 1,351,106 single, legitimate, live and stillborn babies born in England and Wales in 1949 and 1950; and to the deaths of these babies in the first year of life. In addition information is included about the deaths in the second year of life of those born in 1949. Multiple births (i.e., twins, etc.) and illegitimate babies are not considered. Together they formed about 7 per cent of all the births in 1949 and 1950.

METHOD OF PRESENTATION

The main results are presented in Table I (which for convenience is placed at the end), and summarized diagrammatically, in Figures 1 and 2. Figure 1 shows how the mortality varies with the mother's age in families of a particular size. Figure 2 shows the corresponding variation with family size for mothers of a particular age. Both diagrams use the same information, presenting it from complementary points of view.

Each figure has six sections corresponding to stillbirths and to deaths at five stages after birth—the first week of life, the next three weeks (thus completing the conventional "neonatal" period), the remainder of the first six months, the second six months and, finally, the second year of life. These periods have been chosen after detailed analysis of the data to bring out what seemed to be the main changes in pattern.

For clarity mothers having their second and third babies have been grouped together in Figure 1, as have mothers having a fourth or later child. Similarly mothers aged 16–24, 25–29 and 30 and over have been grouped together in Figure 2. These amalgamations have also been chosen after careful scrutiny of the data.

* This is the seventh in a series of articles reporting an enquiry made jointly by the Social Medicine Research Unit, Medical Research Council, and the General Register Office. These articles (see References) were prepared by the Unit in collaboration with the General Register Office, and have been approved for publication by the joint working party responsible for the enquiry.

† The parity of the mother is defined here as the number of children she has borne—surviving, dead or stillborn—including the present one. The phrase "size of family" is also used in this sense.

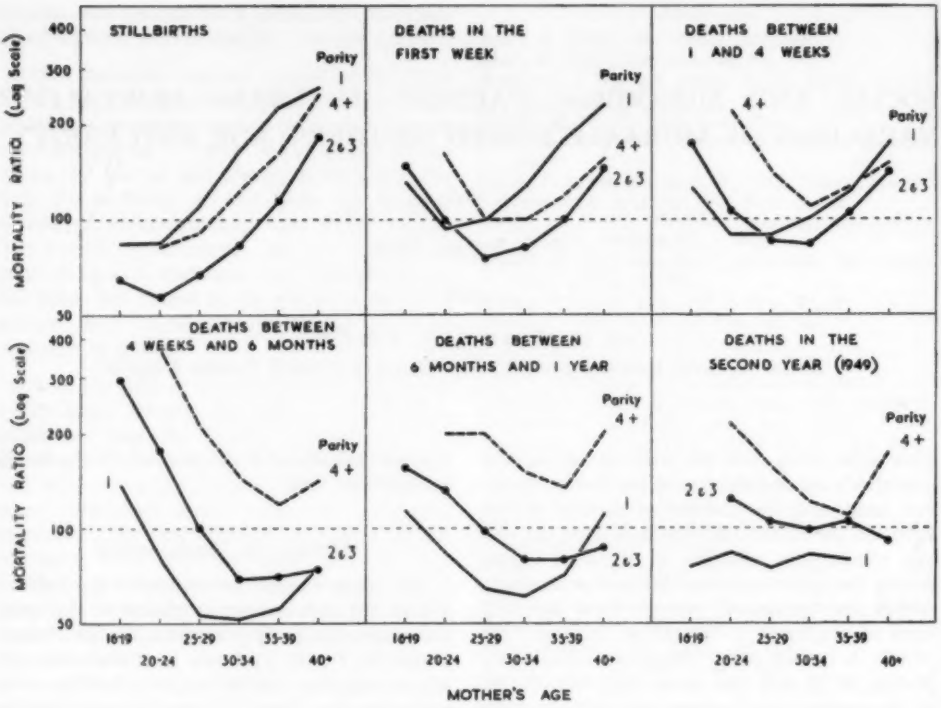

FIG. 1

Variation with the mother's age of the stillbirth rate and mortality rates in the first two years of life (mothers of different parities compared). Single, legitimate births in England and Wales, 1949 and 1950. Rates have been expressed as mortality ratios—see text.

The detailed figures are available in Table I.*

The points that are plotted in the diagrams correspond, not to the crude *rates* given in the Table, but to mortality Ratios calculated from these *rates*. In each section the overall mortality *rate*, for births to mothers of all ages and parities, is taken as 100, and the mortality for births to mothers of a particular age and parity is represented as a proportion (percentage) of this overall mortality. For example, the overall mortality *rate* in the first week of life for births to mothers of all ages and parities is 13·1 per thousand. For births to mothers aged 40 and over having a first baby the *rate* of death in the first week is 29·7. If 13·1 is taken as 100, 29·7 becomes 227 and this is the value that is plotted in Figure 1. The mortality Ratio is used rather than the *rate* because attention is paid here to the variation of mortality within each stage. If crude *rates* were chosen the scale would obscure even

* In spite of the large numbers of births concerned in this enquiry some of the rates are calculated from relatively small numbers. In extreme categories (e.g., mothers aged 45 and over, or with 10 or more children) the rates are not very "reliable" in the statistical sense. For example, the rate of 45·1 for stillbirths born to mothers aged 45 and over having a first child, depending as it does on only 12 stillbirths in the two years, is likely to be different from the rate calculated from the data for the next two years, even in the absence of a real secular change in the stillbirth rate. A figure of 65, for instance, would not be surprising. Rates in the main body of the table are of course much more reliable.

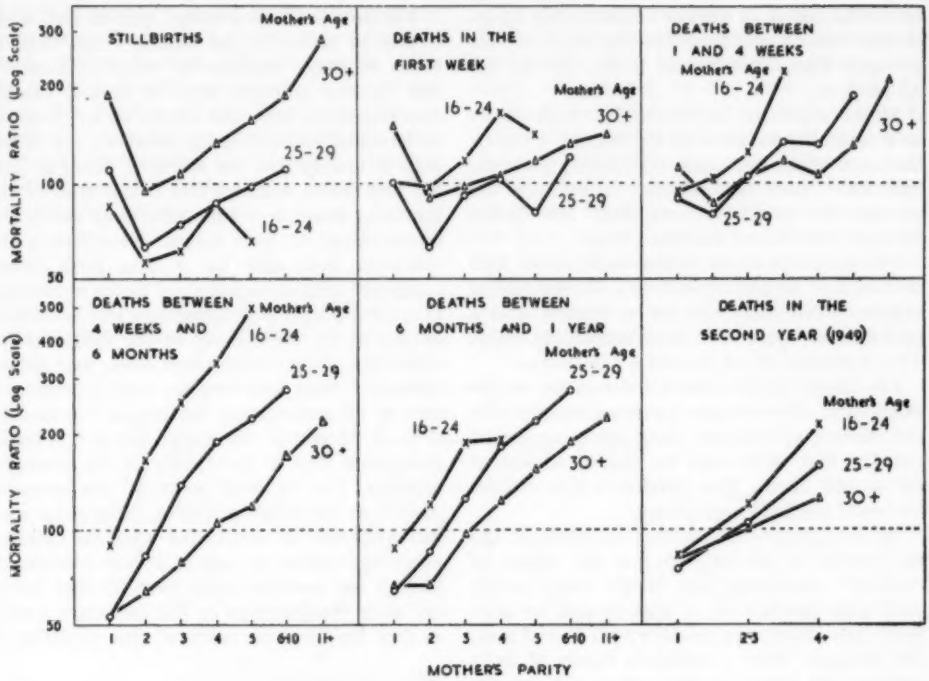

FIG. 2

Variation with the mother's parity of the stillbirth rate and mortality rates in the first two years of life (mothers of different ages compared). Single, legitimate births in England and Wales, 1949 and 1950. Rates have been expressed as mortality ratios—see text.

large proportionate variations in the smaller *rates*. Care should nevertheless be taken not to interpret the Ratios as *rates* and to bear in mind the fact that mortality *rates* in the different sections are very different, the heaviest mortality amongst live born babies occurring, of course, in the first week. Thus the overall mortality of 13·1 per thousand in the first *week* of life compares with 2·3 per thousand in the whole of the second year.

Finally, the Ratios are plotted on a logarithmic scale so that, for instance, the difference between a Ratio of 50 and one of 100 appears as important as the difference between 100 and 200, instead of half as important, as it would appear if plotted on an ordinary linear scale.

RESULTS

Two Contrasting Patterns

Mother's Age—In Figure 1, which shows how mortality varies with the mother's age, there are two main contrasting patterns. The first is the stillbirth pattern, the second the pattern of mortality for children aged between one month (4 weeks) and 6 months.

The *stillbirth* pattern is familiar—after the mother has reached 20 years of age or so the risk increases as she gets older. This is evident for all parities.

The contrasting pattern for the mortality in the period *1–6 months* is less familiar, showing the highest Ratios now for the youngest mothers, the risk falling as the mother gets older until

about the age of 30 when it begins to rise again, though not to anything like the levels of the youngest ages. This pattern is also evident for all parities.

Mother's parity—In Figure 2, which shows how mortality varies with the mother's parity, there are again two main contrasting patterns, and once more the contrast is between the pattern for stillbirths and that for deaths between one and six months of age.

For *stillbirths* there is the well-known high risk for first births followed by a fall for second babies, which show the lowest Ratios, and a gradual rise again with each succeeding baby. This is evident in all maternal age-groups.

For deaths in the period *1–6 months*, on the other hand, the mortality increases steadily with the number of children, there being no special risk for first births and no special advantage for second births. This pattern is also evident for each mother's age-group.

Age and parity—Combining the effects of age and parity, it can be seen that the babies of "elderly" primiparae and of the older women with large families are at highest risk for stillbirth (first children of mothers aged 40 and over, for instance, have a stillbirth Ratio of 262), whereas for deaths in the period 1–6 months the children of young multiparae are the vulnerable group (the 3rd children of mothers aged 16–24 have a mortality Ratio at this stage of 252). On the other hand the lowest stillbirth Ratio is for 2nd babies of mothers aged 20–24 (55), and the lowest Ratio for the period 1–6 months is for the first children of mothers aged 30–34 (51).

Intermediate Patterns

With the two main patterns in mind it can be seen that in the neonatal period, the first four weeks, intermediate patterns exist. In respect of the mother's age (Fig. 1) it is as though each pattern contributed its share in this transitional period. Moreover, in the first week of life the contribution of the stillbirth pattern (high Ratios for older mothers) is clearer than in the rest of the neonatal period, whereas the 1–6 months pattern (high Ratios for younger mothers) is more evident in the latter three weeks than in the first.

The double "contribution" can be seen more clearly in terms of the mother's age than in terms of parity because the effect of mother's age on the stillbirth rate is almost exactly opposite to its effect on deaths at 1–6 months. In terms of parity (Fig. 2), however, the difference is mainly that the stillbirth Ratio is high for first births whereas this is not true of the mortality Ratio at 1–6 months. High parity is a disadvantage at both stages. Nevertheless the relatively high risk for a first birth (when compared with second or third births to mothers of a similar age) is progressively less noticeable as one looks successively at the diagrams for stillbirths, deaths in the first week, and deaths between 1 week and 4 weeks, until it cannot be seen at all in deaths in the period 1–6 months (Fig. 2). Moreover this higher risk in first births disappears first in the babies of the youngest mothers. For in both parts of the neonatal period, as the diagram shows, there is no such increased risk for first births when the children of women under the age of 25 are considered, though for mothers aged over 25 first births are at a disadvantage in this neonatal period as they are from the point of view of stillbirth.

After Six Months

The patterns for deaths in the second half of the first year and in the second year tend to be weaker versions of the pattern at 1–6 months. The effects of the mother's age and the size of her family thus appear to become progressively less important, and in the second year, though size of family still seems to have an influence, the effect of the mother's age is hardly noticeable except in the larger families.

Summing-up

To sum up, there is a considerable variation in perinatal and infant mortality for babies of mothers of different ages and parities, and there seem to be two distinct patterns of relationship between this early mortality and mother's age and parity. One of these patterns is for stillbirths and the other is for deaths between 1 and 6 months. In particular, older women are the most likely to have stillbirths whereas the youngest mothers are the most likely to lose their babies in the post-neonatal period. The

pattern of mortality in the intervening neonatal period appears to be a compound of the two main patterns in these adjacent periods. After the age of 6 months and up to the age of two years the pattern of childhood mortality in relation to maternal age and family size bears a general resemblance to the pattern between 1 month and 6 months but it becomes progressively less marked.

Early Neonatal Mortality

Deaths in the First Few Days and Hours

As has been stated the emphasis in this paper is on perinatal mortality, i.e., stillbirths and deaths in the first week. It is not possible with the present data to subdivide stillbirths by length of gestation at the time of delivery, illuminating as this would be (Kohl, 1955). It is, however, possible to examine the pattern of mortality for babies dying at different stages in the first week—in the first day, for instance, and indeed for those stated to have died in the first three hours. The numbers of deaths in the first hour or two are too small for definite conclusions to be drawn. Figure 3 therefore shows the pattern for stillbirths and for mortality in the first three hours, the rest of the first day,

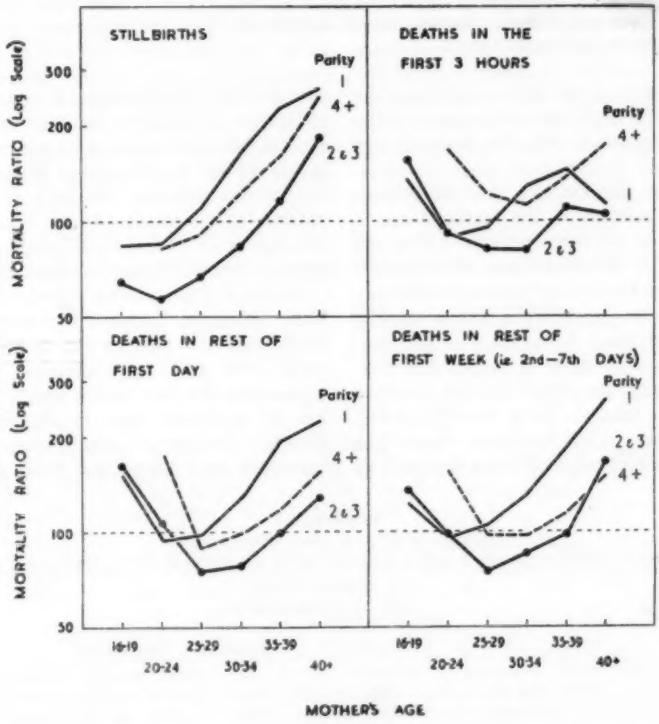

FIG. 3

Variation with the mother's age of the stillbirth rate and mortality rates in the first three hours of life, the remainder of the first day and the remainder of the first week (mothers of different parities compared). Single, legitimate births in England and Wales, 1949 and 1950. Rates have been expressed as mortality ratios—see text.

TABLE II
Mortality in the First Hour of Life
Single, Legitimate Births. England and Wales, 1949 and 1950

Mother's Parity (No. of Children Borne)	Mother's Age (Years)							Total
	16–19	20–24	25–29	30–34	35–39	40 and Over	Not Stated	
1	1·4	1·0	1·2	1·5	1·9	(1·5)	—	1·2
	(63)	(217)	(188)	(82)	(45)	(8)	(1)	(604)
2 and 3	(1·4)	1·0	0·9	0·8	1·2	1·2	—	0·9
	(9)	(126)	(209)	(117)	(95)	(21)	(2)	(579)
4 and over	0	2·1	1·3	1·3	1·5	2·1	—	1·5
	(0)	(13)	(51)	(69)	(82)	(55)	(0)	(270)
Not stated	(0)	(1)	(0)	(0)	(1)	(0)	(1)	(3)
Total	1·4	1·0	1·0	1·1	1·4	1·7	—	1·1
	(72)	(357)	(448)	(268)	(223)	(84)	(4)	(1,456)

The top line for each parity (or group of parities) is the rate per thousand live births.
The second line, in brackets, shows the number of deaths.
Where there are fewer than 10 deaths, the rates are also in brackets.
For definitions see the footnotes to Table I.

and the remainder of the first week (i.e., the second to seventh days). In each case it is the pattern of the variation with the mother's age which is shown.

It is clear from this diagram that the pattern of mortality in relation to the *mother's age* is much the same at all three periods within the first week, and is different from the stillbirth pattern. In particular the existence of a relatively high Ratio for young mothers is just as marked for deaths under three hours as it is for later deaths. With this in mind it is perhaps permissible to examine the rather slender evidence for even earlier deaths—Table II. This table, dealing with deaths in the first hour, shows that the pattern gives every sign of being the same as for the first three hours. In other words, the difference in pattern between stillbirths and neonatal deaths seems to be present from birth, or, in terms of the earlier discussion of two contrasting patterns, the part of the neonatal pattern which appears to be "contributed" by the second or "1–6 month" pattern seems to be present from birth, and is absent in stillbirths.

In terms of the *mother's parity* there was very little difference between the pattern for stillbirths and the pattern for deaths in the first week. The only real difference was that the excess risk for first births which was apparent for *all* maternal ages in stillbirths was not apparent for *young* mothers when deaths in the first week were considered. Table III shows that

TABLE III
Mortality in the First Three Hours of Life
Rates per 1,000 Live Births. Single, Legitimate Births, England and Wales, 1949 and 1950

Mother's Age (Years)	Mother's Parity (No. of Children Borne)				Total
	1	2 and 3	4 and Over	Not Stated	
16–19	2·9	3·3	—	—	2·9
	(129)	(21)			(150)
20–24	1·9	2·0	3·6	—	2·0
	(437)	(258)	(23)	(1)	(719)
25–29	2·1	1·8	2·6	—	2·0
	(330)	(430)	(105)	(1)	(866)
30–34	2·8	1·7	2·4	—	2·1
	(155)	(255)	(129)		(539)

(Numbers of deaths are shown in brackets)

this difference between stillbirths and first week deaths also occurred in deaths in the first three hours.

Prematurity

Although prematurity is such an important consideration in perinatal mortality the design of the present enquiry, relying as it does on birth and death certificates, where there is no information about birth-weight, rather than on notification of births, where this information is given, precludes the linking of the birth-weight of the babies to their survival. The next best thing is to obtain the distribution of birth-weights according to the mother's age and parity for large populations of complete areas (i.e., not merely hospital births) in England and Wales. So far as is known only one such set of data is published, namely that of McKeown and Gibson (1951) for the births of Birmingham in 1947. These data, recalculated to show the percentage of births which were premature (i.e., weighed under 5½ pounds), are shown in the first part of Figure 4. In addition, Professor Dugald Baird has kindly made available similar data for Aberdeen in the period 1948–56 which is reproduced in the second part of the same figure, and a recent publication of the United States National Office of Vital Statistics (1958) makes possible the corresponding analysis given in the third part of the figure. What these data lack in direct relevance to the present enquiry is made up by their unanimity; though they do not apply to the population under study they do apply to populations whose perinatal mortality is at much the same level and shows much the same variations with maternal age and parity as in England and Wales (Yerushalmy, 1938; City of Birmingham, 1951; Baird, Walker and Thomson, 1954). And the patterns these three sets of data reveal are essentially similar. It will be seen in particular by comparison with Figures 1 and 3, that the variation in the proportion of births which are premature by weight (5½ pounds or under) in each of these populations is similar to the

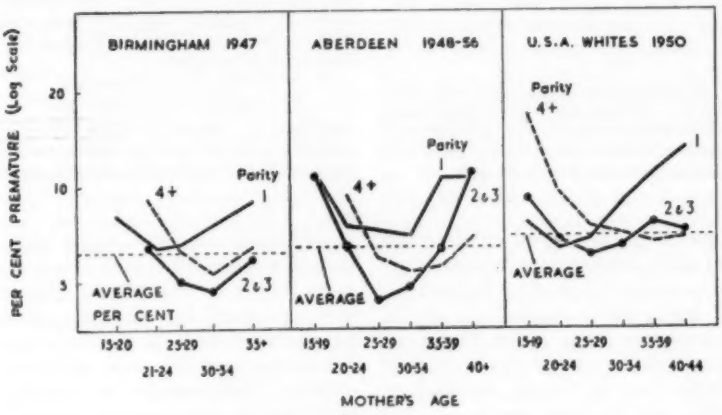

FIG. 4

Variation with the mother's age in the proportions of premature births (mothers of different parities compared). Results from various studies—see text. Definitions of prematurity and the groups of births included in the various experiences are as follows:

Birmingham: "Premature"=weighing less than 5½ pounds at birth: single births, live and stillborn.

Aberdeen: "Premature"=weighing 5½ pounds or less at birth: single, legitimate, live births.

U.S.A. Whites: "Premature"=weighing 2,500 g. (≃5½ pounds) or less at birth: all live births.

variation of the mortality Ratio in the first week and different from the variation of the stillbirth Ratio. That is to say, both the young multiparae and the "elderly" primiparae are specially liable to have premature babies (and young primiparae do not have a higher proportion than other young mothers).

Another approach to the problem of prematurity, this time using the data of the present enquiry, is shown in Figure 5, where the

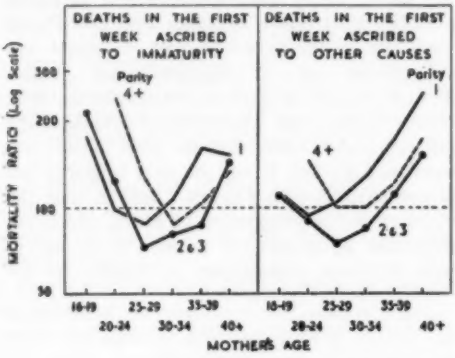

FIG. 5

Variation with the mother's age of mortality rates in the first week ascribed to "Immaturity" and to other causes (mothers of different parities compared). Single, legitimate births in England and Wales, 1950. Rates have been expressed as mortality ratios—see text.

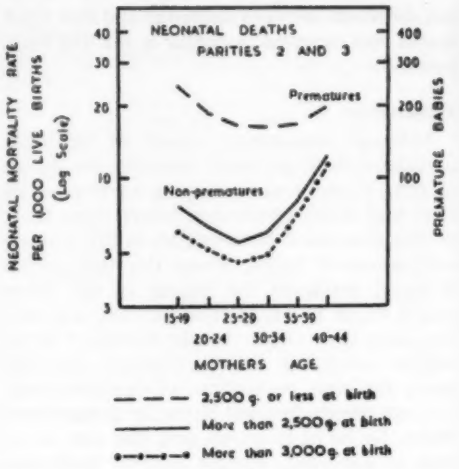

FIG. 6

Variation with the mother's age of the neonatal mortality rate (children of birth weights 2,500 g. or under compared with those of birth weights over 2,500 g. and over 3,000 g.). Live births in U.S.A., January–March, 1950. Whites only. Mothers of parities 2 and 3. Neonatal mortality per 1,000 live births. N.B.—The mortality of children whose birth weights were 2,500 g. or under should be read on the right-hand scale—which is ten times greater than the left-hand scale.

2,500 g. $\simeq$ 5½ pounds.
3,000 g. $\simeq$ 6·6 pounds.

Although, for reasons of space, this figure has been confined to second and third births, the picture is much the same at each birth order, including the first.

Mortality Ratio in the first week of life which is ascribed on death certificates to "immaturity" is related to the mother's age. As a contrast the remainder of deaths not so ascribed are shown. The characteristically high Ratio in young mothers, particularly for multiparae, is certainly more noticeable for the deaths ascribed to immaturity than for the other deaths.

So far the variations in relation to the mother's age of the proportion of premature births and of the mortality actually ascribed to "immaturity" have been described. Figure 6 shows yet a different type of evidence, namely the mortality from *all causes* amongst premature babies (weighing 2,500 g. or 5½ pounds and under at birth) compared with the mortality of non-premature babies. These data are from the same source of United States vital statistics as in Figure 4. Second and third babies only are considered for the sake of clarity, and because they show the relatively high mortality for young mothers more definitely than first children. The whole of the neonatal period is used because, unfortunately, information for the first week only is not available. (This cannot matter much since five out of six deaths in the first four weeks occur in the first week and the variation in neonatal mortality as a whole is very similar to the variation of mortality in the first week.) Again the high rate for young mothers is more noticeable amongst the premature babies than amongst the non-premature.

These three sets of evidence show three things:

(*a*) That the children of young multiparae and of elderly primiparae are more than usually likely to be premature (Fig. 4).

(*b*) That by the criterion of death certificate "Cause", the children of these two groups of women (but particularly the young multiparae) are more likely than the others to die of "immaturity" in the neonatal period (Fig. 5, first part).

(*c*) That of all premature babies (5½ pounds or less) those born of young mothers are the most likely to die (Fig. 6, top line).

In spite of these three facts, the shape of the neonatal mortality curves in relation to the mother's age, though clearly related to immaturity, is not entirely explained by the distribution of immature births. In other words, though the pattern may be less recognizable, particularly that part of it which shows relatively high rates for the children of young mothers, it is still discernible in the mortality of babies which weigh more than 5½ pounds (and in fact of those which weigh more than 6·6 pounds) and in the mortality *not* ascribed on death certificate to "Immaturity" (the bottom lines of Figure 6 and the second half of Figure 5).

Furthermore, since the risk of prematurity and of death in the first week is high in young multiparae but the stillbirth rate is not, the relationship of prematurity with stillbirths differs from its relationship with early neonatal mortality—though a high proportion of stillbirths as well as of neonatal deaths are premature.* The variation with the mother's age of the stillbirth and neonatal mortality rates in multiple births is also of interest here for a high proportion of multiple births are premature. Both stillbirth and neonatal mortality rates are high in multiple births, and they are specially high in the multiple births of young mothers, but the effect is much more noticeable in neonatal deaths than in stillbirths (cf. Fig. 8 of the first paper in this series, Morris and Heady, 1955a).

* England and Wales, 1956

Category	Still-births	1st Day Deaths	1–27 Day Deaths
Total†	16,405	5,144	6,635
In prematures .. .. (5½ pounds or under at birth)	8,305	3,880	3,054
Per cent premature of total	51	75	46

(Ministry of Health, 1957; Registrar General, 1957)

† Totals are for registrations, figures for prematures are for notifications, but differences are unimportant.

Certified Causes of Death in the Neonatal Period

The pattern of mortality in the neonatal period in relation to the mother's age cannot be clearly accounted for by the causes of death as certified, at least not to the extent that the trend for younger mothers is mainly accounted for by one group of causes and the trend for older mothers by another group. Table IV shows, however, that if "young multiparae" are taken as mothers under twenty having a second or later child together with mothers under twenty-five having a third or later child, and "elderly primiparae" are defined as primiparae aged 35 and over, the group of causes—congenital malformations, birth injury, and disorders arising from maternal toxaemia—cause a higher *proportion* (42 per cent) of deaths amongst "elderly primiparae" than amongst "young multiparae" (21 per cent). This group of causes is classically associated with stillbirths. Another group of causes—respiratory diseases, enteritis and diarrhoea and accidents—accounts for a higher *proportion* of deaths in "young multiparae" (12 per cent) than in "elderly primiparae" (7 per cent). This group of causes is of course particularly associated with deaths in the post-neonatal period. To some extent, then, causes associated with stillbirths are associated with the right hand or "older" part of the neonatal mortality curve in relation to the mother's age, and the post-neonatal causes with the left hand or "younger" part of the neonatal mortality curve. This association should not, however, be over-emphasized since in fact deaths from *each* of these causes of death, considered separately over the whole range of mothers' ages, show the neonatal pattern of high risk for the youngest and oldest mothers. Finally it is of interest that in Table IV deaths

TABLE IV

Distribution of Neonatal Deaths by Cause in Two "Vulnerable Groups" Single, Legitimate Births, England and Wales, 1950

Cause of Death	Young Multiparae		"Elderly" Primiparae		All Mothers	
	No.	Per cent	No.	Per cent	No.	Per cent
"Post-neonatal" Causes:						
Respiratory diseases	38	8·3	25	6·4	773	7·4
Enteritis and diarrhoea	7	1·5	1	0·3	76	0·7
Accidents	10	2·2	0	0	96	0·9
Immaturity	173	37·6	101	25·9	2,933	28·2
Causes associated with Stillbirths:						
Congenital malformations	55	12·0	68	17·4	1,722	16·6
Birth injury	40	8·7	75	19·2	1,518	14·6
Neonatal disorders arising from maternal toxaemia	3	0·7	23	5·9	231	2·2
Other Causes:						
Asphyxia and atelectasis	78	17·0	65	16·7	1,868	18·0
Haemolytic disease	26	5·7	2	0·5	426	4·1
Haemorrhagic disease	6	1·3	8	2·1	148	1·4
Others	24	5·2	22	5·6	594	5·7
All causes	460	100·2	390	100·0	10,385	99·8

Definitions of Vulnerable Groups:

Young Multiparae = { Mothers aged under 20 with one or more previous children. / Mothers aged under 25 with two or more previous children.

"Elderly" Primiparae = Mothers aged 35 or over having a first child.

ascribed to Immaturity behave like post-neonatal deaths in that they cause a higher proportion of deaths amongst "young multiparae" (38 per cent) than amongst "elderly primiparae" (26 per cent); thereby, so to speak, being associated with the causes known to be related to the external social environment of the child more than with the causes of intra-uterine death.

Social Class

Following this line of thought it is interesting to examine the social class distribution of neonatal deaths. Wives of men in semi-skilled and unskilled occupations (social classes IV and V) tend to have their babies at younger ages than the wives of men in social classes I and II (cf. Daly, Heady and Morris, 1955). Since mortality rates and the proportion of immature births are both higher in classes IV and V it might be thought that some part of the excess neonatal mortality in the babies of young mothers would be accounted for by this fact. Figure 7, dealing

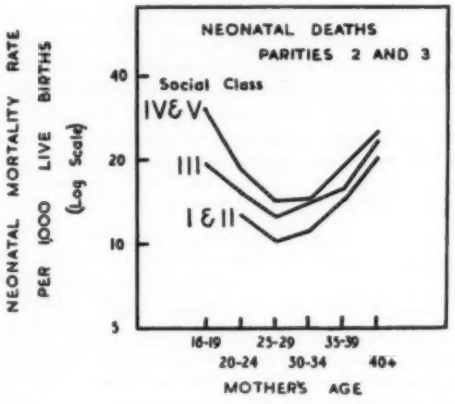

FIG. 7

Variation with the mother's age of the neonatal mortality rate in children in different social classes. Single, legitimate births in England and Wales, 1949 and 1950. Mothers of parities 2 and 3. Classification by "Social class" is based on the father's occupation at the time of the birth.

with neonatal mortality in second and third babies for reasons explained above, shows the rates. The same pattern that has been observed for all births is apparent, perhaps a little more so, for births in classes IV and V. It is present, too, in class III. (The number of mothers under 20 in social classes I and II is so small that no reliable rates can be produced even using two years data for the whole country.) This shows that the social class distribution of births to mothers of different ages does not account for the pattern of variation. It certainly does not mean, however, that a "social" cause of the variation is excluded. This point will be discussed later.

Table V approaches the problem in an analogous way to Table IV. It will be seen that the social class trend is clear in "young multiparae" (defined as before) whereas, apart from a high rate in social class V, there is no trend in "elderly primiparae".

It is perhaps worth mentioning in passing that though the neonatal mortality amongst babies conceived before marriage is high,* and such babies are well known to be commonest in young mothers, the pattern of neonatal mortality in relation to mother's age is not simply accounted for by this fact, for the excess mortality in babies of young mothers is most noticeable in multiparae and prenuptially conceived babies are nearly always first babies.

TABLE V

Social Class Variation of Neonatal Mortality in Two "Vulnerable Groups"

Single, Legitimate Births, England and Wales, 1950

Social Class of Father	Young Multiparae		"Elderly" Primiparae		All Mothers	
I ..	0	17·5	28·1	29·1	11·6	13·8
	(0)		(24)			
II ..	20·2		29·5		14·4	
	(18)		(84)			
III ..	19·7		27·2		15·9	
	(214)		(190)			
IV ..	25·6		28·9		17·5	
	(126)		(47)			
V ..	26·9		38·7		18·9	
	(102)		(44)			
All classes	22·3		28·8		16·1	
	(460)		(390)			

The top line for each social class is the rate per thousand live births.

The second line shows the number of deaths.

Definitions of Vulnerable Groups:

Young multiparae = Mothers aged under 20 with one or more previous children. Mothers aged under 25 with two or more previous children.

"Elderly" primiparae = Mothers aged 35 or over having a first child.

COMMENT

It has been shown that mortality in the neonatal period is related to the mother's age and her parity in a way which seems to combine the characteristic pattern of the variation for stillbirths with the characteristic pattern for postneonatal deaths. Intuitively this might, perhaps, have been expected, but it was not to be expected that the characteristics of the pattern for postneonatal mortality—the relatively high rate for the babies of young multiparae—should apply, so far as can be seen, to deaths which occur immediately after birth. The contrast is with the stillbirth rate where there is no such high rate for young multiparae; in fact their rates are particularly low. This difference will be briefly considered.

There is, of course, no warrant to conclude definitely that there is a sharp difference between *all* stillbirths and all neonatal deaths in this respect. There may yet be a small sub-group of stillbirths which are relatively common in young multiparae. Such a minority might be the stillbirths which occur very near term or might be included in those stillbirths where the death occurs during birth. An analysis by maternal age and parity of stillbirths of different lengths of gestation, or, at the least, according to whether they were ante- or intra-partum would be rewarding from this point of view.

* The neonatal mortality of single, legitimate babies born in the first 9 months of marriage in England and Wales in 1949 was 22·4 per 1,000 live births compared with 16·4 for all single, legitimate births, and 27·0 for single, illegitimate births.

It is, however, not unreasonable to expect some important differences between deaths *in utero* or during labour and deaths immediately afterwards if only because of the switch-over to pulmonary respiration. The demonstrated relationship (Turnbull and Baird, 1957) between advanced maternal age and poor foetal oxygenation would be expected to affect the stillbirth rate much more than the neonatal mortality rate. The steady increase of the stillbirth rate as the mother's age increases is consistent with this expectation, the increase being more marked than in neonatal mortality. Moreover, the relatively high neonatal mortality rate of the infants of young multiparae is consistent with failure to establish a new system of respiration, for it has been shown that neonatal deaths from "immaturity" are relatively common in the infants of such mothers (Fig. 5), and neonatal fatalities due to "hyaline membrane" and "pulmonary syndrome of the newborn" (Bound, Butler and Spector, 1956) are especially associated with immaturity. The newly-born infant, moreover, is exposed to more potential infection than the protected foetus and there is accumulating evidence (Smith *et al.*, 1956) that infection may be an important cause of these very early deaths.

The sharp difference between the age-parity pattern for immaturity and that for stillbirths, considering that about half of all stillbirths are immature by weight, has already been mentioned. The contrast surely underlines the fact, self-evident in some ways, that stillbirths and neonatal deaths are related to immaturity in different ways. Whereas it may be useful to regard immaturity as at least an intermediate cause of neonatal death, it can hardly be said to *cause* a stillbirth except, possibly, intrapartum. Stillbirths which are "premature" in the sense of occurring before term may, in fact, be born early, and hence probably also underweight, because the foetus has died *in utero*.

The concept of "perinatal mortality", i.e., stillbirths together with deaths in the first week, is a useful one. This is partly because there is a distinct group of "perinatal" causes of death (e.g., birth injury, "asphyxia and atelectasis", "immaturity") which are not so important once the relatively dangerous period around birth is safely past. Further, from the point of view of the comparison of international vital statistics, where there are (or have been) administrative differences in the definition of what is a "stillbirth" and what a "live birth" (in France, Belgium and Spain, for instance, until recently the definition of a stillbirth included infants born alive but who died before registration of birth), it is an idea which must command acceptance. By the combination of deaths just before and just after birth such difficulties can be conveniently avoided. The present evidence shows, however, that the two main components of the perinatal period—stillbirths and deaths in the first week—are differently related to maternal age and parity, and also that prematurity, regarded by many as the key factor in any further reduction of perinatal mortality, is, in some way, connected with the difference. It is therefore possible that too great an insistence that perinatal deaths form a single clinical entity may mean that some clues to the causes of death in the perinatal period are overlooked and that some questions are not raised.

The relative disadvantage in the early neonatal period of the babies of young mothers needs to be seen in numerical perspective. It is not suggested that the mother's age is one of the most important variables in neonatal mortality. Analyzed in terms of the mother's age the highest rate is never more than two and a half times the lowest rate for mothers of the same parity. Maternal age is not so important in neonatal deaths as it is, for instance, in stillbirths where the rates for the oldest mothers of a given parity can be as much as four times the lowest rates: or as the youth of the mother in post-neonatal mortality where the ratio of extreme rates within a given parity can be nearly as great as for stillbirths. Nor can it be compared in importance with such factors as multiple birth or immaturity itself in neonatal mortality. The presence of a history of previous infant loss is also a more useful indicator of the risk of a further neonatal death than is the mother's age (Gardiner and Yerushalmy, 1939; Schlesinger and Allaway, 1955). There is nevertheless a group of mothers here—young mothers with

several small children—which may repay study, and who should certainly be receiving special care, especially since their babies become a highly "vulnerable" group a little later on (Morris, 1957).

The fact that children of the same group of mothers are at high risk of dying later in the first year, when environmental causes of death are assumed to be at their most powerful, suggests that the causes of the earlier deaths in the children of the same women may also be largely external and environmental. That a group of women defined in similar terms is at relatively high risk within each social class (cf. Fig. 7) is no reason for rejecting an "environmental" explanation of the risk, for the qualities which distinguish the young mother who has her babies at relatively short intervals may affect the chances of survival of her child in *any* class.

Direct information about the characteristics of young women with relatively large families is scanty. A higher proportion than average of such mothers have their babies at home (Heady and Morris, 1956); the quality of maternal care, so strongly implicated by Spence and his colleagues (1954), was shown to be poorer in large families but no data were presented about maternal age. More indirectly: large families of young children are commoner in social classes IV and V than in I and II; amongst primiparae in social classes IV and V the average of maternal intelligence and education, of height and "physical health" is poorer than in classes I and II (Baird and Scott, 1953; Illsley, 1955); young primiparae who were short (under 5 feet 1 inch) went on to have more children more quickly than young women who were tall; and women having fourth and later babies in hospital in Aberdeen were shorter than the primiparae on average (Baird and Scott, *loc. cit.*). Moreover there is a greater spread of infection in large families with small children (Badger *et al.*, 1953; Brimblecombe *et al.*, 1958). All of which suggests, though it does not prove, that there is a concentration of poor qualities from the child-bearing and child rearing point of view in young mothers who have a large number of children for their age—and it may be that this applies within social classes. In fact a possible interpretation of the high neonatal and post-neonatal rates in the children of young mothers with several small children is that these rates reflect the social background of the women (not simply their present "social class"), and the quality of the care they provide for their children (Baird and Illsley, 1953; Illsley, 1955; Drillien, 1957). The suggestion is that inferior maternal physique and health, together with a high prematurity rate, go with early marriage, rapid childbearing, and relatively poor maternal care in *any* social class.

In neonatal mortality prematurity is probably the key factor; and since the neonatal mortality pattern in relation to maternal age and parity is much the same in each class, it would be surprising if the variation of prematurity with age and parity were not also substantially the same in each social class. This remains to be shown. The prematurity rate as well as the neonatal mortality rate has, however, been shown to be higher in young mothers with large families, taking all classes together; and in this respect therefore also resembles the post-neonatal mortality rate. Moreover, prematurity shows a strong class gradient as does post-neonatal mortality. Yet in recent years the post-neonatal mortality rate has declined substantially while there is no evidence of any decrease in the rate of prematurity. It is generally agreed that the fall in the post-neonatal mortality rate is due to the control of infections—both by reducing exposure of infants and by mitigating the consequences of the infections to which they are exposed (cf. Knox and Mackintosh, 1958). Infection presumably plays an unimportant part in the causation of prematurity, and, insofar as the variation in the rate of prematurity reflects the social characteristics of the mother concerned, it must be brought about by other factors, possibly those related to the care of the mother herself in pregnancy and before.

Thus the findings of the present enquiry are consistent with an explanation of the high mortality rates among the infants of young mothers with large families in "social" terms such as the standards of care they provide for themselves and for their infants. It does not, of course, follow that such factors provide the whole explanation. There is room for a part of the explanation at least along more purely

physiological lines. Too early and too rapid child bearing, for instance, are conceivably related to the incidence of premature birth without invoking any social selection of mothers as an explanation—maternal age and parity could, in part, be operating here directly as "biological" variables as well as expressing indirectly the working of "social" factors. At present there seems to be no clear way of deciding the relative importance of the two types of explanation; and this is likely to continue while we remain ignorant of the main causes of neonatal mortality and, in particular, of the mechanisms which produce underweight and premature babies.

Summary

The relationships between (*a*) the mother's age and parity and (*b*) the stillbirth rate and the mortality rates of infants of different ages within the first two years of life, are shown for the single, legitimate births of England and Wales. The mortality rates up to the end of the first year are for the 1,350,000 such children born in 1949 and 1950; those in the second year for the births of 1949.

Maternal age and parity are quite differently related to stillbirth and to the chances of an infant dying during the post-neonatal period.

The *stillbirth* rate rose with maternal age from 16 per 1,000 at 20–24 years to 47 per 1,000 at 40–44 years of age. The average stillbirth rate was 21. The rate was high in primiparae, low in mothers of second and third children and rose again with greater parities. Thus, "elderly primiparae" showed a particularly high rate (e.g., 56 per 1,000 in primiparae aged 40–44); and so did "grand multiparae" (e.g., in mothers of 6th–10th children the rate was 39). The lowest identified stillbirth rate in terms of age and parity was 12, that of mothers aged 20–24 bearing a second child.

Post-neonatal mortality (deaths at 4 weeks–1 year) rose with maternal parity, i.e., with the birth rank of the child and size of family; it was 7·9 per 1,000 among first-born children and 20 among 6th–10th births. The average post-neonatal mortality rate was 11 per 1,000. Moreover, post-neonatal mortality was high in children born to young mothers, low when the mother was in her late 20's or in her 30's, and it rose again after that. Thus for young mothers with large families for their age, there were particularly high post-neonatal mortality rates in the infants (e.g., for mothers under 20 years of age second and later-born children showed a rate of 27, as also did the third and later-born children of mothers aged 20–24). The lowest identified rate was 5·8 per 1,000 for first-born infants of mothers aged 30–34. These trends in the post-neonatal mortality rate were sharper in infants aged 1–6 months than in those aged 6 months–1 year.

The pattern of *neonatal* mortality, i.e., deaths in the first 4 weeks of life, resembled that of stillbirth in that there were high rates for the children of "elderly primiparae" (35 per 1,000 for first children of mothers aged 40–44) and of "grand multiparae" (22 per 1,000, where the child was 6th–10th in birth rank). In addition, however, there was evidence during the neonatal period of the post-neonatal distribution of mortality just described, the neonatal mortality rate being high in the children of young multiparae—25 per 1,000 where the mother was under 20 years of age bearing a second and later child and 21 where she was aged 20–24 bearing a third and later child. The average neonatal mortality rate was 16 per 1,000; and the lowest rate by age and parity was 11 per 1,000 in second-born children of mothers aged 25–29.

This tendency to a high neonatal mortality rate among children of young multiparae could be discerned in deaths occurring during the first hours of life and it was evident throughout the neonatal period. Children of young multiparae thus showed a high neonatal mortality rate in the first week of life, in contrast with their stillbirth rate which is low. A difference is thus shown in respect of age and parity between the two main elements—stillbirths and first week deaths—of "perinatal" mortality.

The characteristic pattern of neonatal mortality in relation to maternal age and parity was found in families of the professional classes (the Registrar General's Social Classes I and II) as well as in the families of skilled workers (Class III) and in the families of semi-skilled workers and of labourers (Classes IV

and V); though, of course, all the death rates tended to be lower in Classes I and II than in Classes III, IV and V.

Evidence from other studies is presented which shows that the proportion of babies born premature by weight is particularly high for young multiparae and for the older primiparae; i.e., the pattern is to a large extent similar to that of neonatal mortality.

Young mothers with several children thus have a high prematurity rate and their infants a high mortality in the neonatal and the post-neonatal periods. These mothers and children are a "vulnerable" group which should receive special attention from medical services.

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Stillbirth Rates and Mortality Rates at Five Two Years
Single, Legitimate Wales, 19

Mother's Parity (No of Children Borne)	Stage	16–19		20–24		25–29	Mother's 30–34
		Deaths	Rate†	Deaths	Rate†	Deaths	
1	Stillbirths	813	17·8	4,112	17·9	3,834	
	Deaths in the first week	778	17·4	2,791	12·4	2,121	
	Deaths between 1 and 4 weeks	175	3·9	622	2·8	441	
	Deaths between 4 weeks and 6 months	484	10·8	1,378	6·1	655	
	Deaths between 6 months and 1 year	153	3·4	561	2·5	306	
	Deaths in the second year*	41	1·8	229	2·0	147	
	Live births‡	44,840		225,096		159,519	55,153
2	Stillbirths	82	13·7	1,253	11·8	2,302	
	Deaths in the first week	114	19·3	1,291	12·4	1,520	
	Deaths between 1 and 4 weeks	31	5·3	330	3·2	414	
	Deaths between 4 weeks and 6 months	132	22·4	1,283	12·3	1,102	
	Deaths between 6 months and 1 year	25	4·2	376	3·6	440	
	Deaths in the second year*	6	—	151	2·8	179	
	Live births‡	5,892		104,487		169,727	90,461
3	Stillbirths	5	—	351	13·1	1,149	
	Deaths in the first week	8	—	404	15·3	874	
	Deaths between 1 and 4 weeks	3	—	101	3·8	234	
	Deaths between 4 weeks and 6 months	13	31·9	512	19·4	787	
	Deaths between 6 months and 1 year	4	—	147	5·6	275	
	Deaths in the second year*	2	—	34	2·7	122	
	Live births‡	407		26,366		72,828	55,261
4	Stillbirths	1	—	97	18·3	491	
	Deaths in the first week	1	—	112	21·6	351	
	Deaths between 1 and 4 weeks	—	—	36	6·9	111	
	Deaths between 4 weeks and 6 months	—	—	137	26·4	383	
	Deaths between 6 months and 1 year	—	—	30	5·8	142	
	Deaths in the second year*	—	—	11	4·7	46	
	Live births‡	28		5,194		26,234	26,948
5	Stillbirths	—	—	13	13·9	194	
	Deaths in the first week	—	—	17	18·4	98	
	Deaths between 1 and 4 weeks	—	—	5	—	38	
	Deaths between 4 weeks and 6 months	—	—	36	39·0	161	
	Deaths between 6 months and 1 year	—	—	6	—	60	
	Deaths in the second year*	—	—	3	—	16	
	Live births‡	2		922		9,165	13,14
6–10	Stillbirths	—	—	2	—	108	
	Deaths in the first week	—	—	6	—	73	
	Deaths between 1 and 4 weeks	—	—	2	—	27	
	Deaths between 4 weeks and 6 months	—	—	5	—	99	
	Deaths between 6 months and 1 year	—	—	2	—	38	
	Deaths in the second year*	—	—	—	—	11	
	Live births‡			187		4,605	13,27
11+	Stillbirths	—	—	—	—	—	
	Deaths in the first week	—	—	—	—	1	
	Deaths between 1 and 4 weeks	—	—	—	—	—	
	Deaths between 4 weeks and 6 months	—	—	—	—	—	
	Deaths between 6 months and 1 year	—	—	—	—	—	
	Deaths in the second year*	—	—	—	—	—	
	Live births‡					11	26
Not stated	Stillbirths	4	—	60	—	68	
	Deaths in the first week	1	—	4	—	4	
	Deaths between 1 and 4 weeks	—	—	—	—	1	
	Deaths between 4 weeks and 6 months	—	—	1	—	2	
	Deaths between 6 months and 1 year	—	—	—	—	—	
	Deaths in the second year*	—	—	—	—	1	
	Live births‡	89		982		1,095	59
Total	Stillbirths	905	17·3	5,888	15·9	8,146	
	Deaths in the first week	902	17·6	4,625	12·7	5,042	
	Deaths between 1 and 4 weeks	209	4·1	1,096	3·0	1,266	
	Deaths between 4 weeks and 6 months	629	12·3	3,352	9·2	3,189	
	Deaths between 6 months and 1 year	182	3·6	1,122	3·1	1,261	
	Deaths in the second year*	49	1·9	428	2·3	522	
	Live births‡	51,258		363,234		443,184	255,1

* Second year deaths amongst the births of 1949 only. † Stillbirth rates per 1,000 live and stillbirths; ... per 1,
‡ The live births amongst which the deaths shown in the table occurred, i.e., the original cahort or post
Mother's age refers to age attained on her last birthday before the present birth
Mother's parity refers to the number of children borne, surviving dead and stillborn (and including the pres... mo
The absence of an entry for deaths or births indicates that there were no such occurrences. *Rates* are not ... w

tes at Five Two Years of Life by Mother's Age and Parity
egitimate Births, England and Wales, 1949 and 1950

	Mother's Age (Years)										
25–29	30–34		35–39		40–44		45+		Not Stated	Total	
aths	*Rate*†	Deaths	*Rate*†	Deaths	*Rate*†	Deaths	*Rate*†	Deaths	Deaths	*Rate*†
34	*34·7*	1,181	*47·9*	304	*55·8*	12	*45·1*	60	12,301	*23·4*
21	*17·0*	559	*23·8*	152	*29·6*	8	—	21	7,369	*14·3*
41	*3·1*	89	*3·8*	28	*5·4*	2	—	2	1,530	*3·0*
35	*4·0*	102	*4·3*	30	*5·8*	2	—	3	2,872	*5·6*
06	*1·8*	50	*2·1*	18	*3·5*	—	—	—	1,189	*2·3*
17	*1·9*	23	*1·8*	3	—	1	—	—	498	*1·9*
159,519	55,153		23,499		5,140		254	754	514,255	
02	*17·0*	1,026	*23·3*	326	*38·0*	19	*47·9*	11	6,582	*15·3*
10	*10·2*	557	*12·9*	169	*20·5*	10	*26·5*	7	4,587	*10·8*
04	*2·4*	139	*3·2*	26	*3·1*	2	—	4	1,162	*2·7*
02	*4·9*	214	*5·0*	39	*4·7*	6	—	6	3,227	*7·6*
10	*2·0*	89	*2·1*	22	*2·7*	1	—	—	1,132	*2·7*
09	*2·3*	50	*2·2*	7	—	—	—	—	496	*2·3*
169,727	90,461		43,092		8,258		378	884	423,179	
09	*18·2*	914	*25·8*	325	*37·4*	28	*65·1*	11	3,805	*18·8*
04	*11·9*	463	*13·4*	143	*17·1*	9	—	10	2,568	*12·9*
04	*2·9*	114	*3·3*	44	*5·3*	4	—	—	658	*3·3*
07	*6·2*	217	*6·3*	54	*6·5*	1	—	3	1,928	*9·7*
05	*3·1*	94	*2·7*	22	*2·6*	1	—	2	714	*3·6*
02	*2·3*	47	*2·7*	12	*2·8*	—	—	2	282	*2·9*
72,828	55,261		34,458		8,371		402	458	198,551	
	23·8	619	*28·4*	323	*47·9*	24	*57·1*	6	2,217	*25·0*
	11·5	317	*15·0*	127	*19·8*	10	*25·3*	3	1,232	*14·2*
	3·5	78	*3·7*	26	*4·1*	3	—	—	349	*4·0*
3	*9·0*	154	*7·3*	50	*7·8*	—	—	6	972	*11·2*
2	*3·6*	69	*3·3*	32	*5·0*	5	—	3	379	*4·4*
2	*2·4*	20	*1·9*	15	*4·7*	—	—	1	124	*2·9*
26,234	26,946		21,171		6,416		396	246	86,631	
	25·9	451	*34·7*	225	*45·1*	28	*75·5*	4	1,264	*29·9*
	13·5	198	*15·8*	89	*18·7*	15	*43·7*	—	595	*14·5*
	3·2	42	*3·3*	17	*3·6*	2	—	—	146	*3·6*
	11·2	88	*7·0*	47	*9·9*	2	—	1	482	*11·8*
	5·0	56	*4·5*	19	*4·0*	2	—	—	209	*5·1*
	3·4	19	*3·1*	12	*4·9*	—	—	—	72	*3·5*
9,165	13,147		12,544		4,769		343	123	41,015	
	29·8	809	*38·4*	597	*51·4*	88	*72·7*	16	2,028	*38·5*
	15·9	336	*16·6*	228	*20·7*	24	*21·4*	10	888	*17·5*
	3·2	81	*4·5*	50	*4·5*	7	—	1	217	*4·3*
	15·7	243	*12·0*	140	*12·7*	13	*11·6*	1	709	*14·0*
	6·0	98	*4·8*	67	*6·1*	14	*12·5*	1	300	*5·9*
	3·0	29	*2·8*	22	*3·9*	1	—	1	84	*3·3*
4,605	13,275		20,251		11,016		1,122	196	50,652	
	46·1	74	*50·1*	135	*64·1*	33	*74·7*	3	258	*59·5*
	—	25	*17·8*	34	*17·3*	10	*24·4*	1	78	*19·1*
	—	8	—	16	*8·1*	2	—	—	27	*6·6*
	—	28	*20·0*	32	*16·2*	5	—	—	69	*16·9*
	—	3	—	16	*8·1*	6	—	—	27	*6·6*
	—	3	—	4	—	1	—	—	9	—
11	269		1,403		1,971		409	17	4,080	
	—	40	—	18	—	2	—	271	501	—
	—	4	—	—	—	—	—	27	42	—
	—	—	—	—	—	—	—	5	6	—
	—	1	—	—	—	—	—	6	11	—
	—	—	—	—	—	—	—	1	2	—
	—	—	—	—	—	—	—	—	1	—
1,095	395		331		95		5	595	3,787	
	23·1	5,114	*31·6*	2,253	*46·7*	234	*66·0*	382	28,956	*21·4*
	12·6	2,459	*15·7*	942	*20·5*	86	*26·0*	79	17,359	*13·1*
	2·8	557	*3·6*	207	*4·5*	22	*6·6*	12	4,095	*3·1*
	6·3	1,047	*6·7*	392	*8·5*	29	*8·8*	26	10,270	*7·8*
	2·7	459	*2·9*	196	*4·3*	29	*8·8*	7	3,952	*3·0*
4	*2·3*	191	*2·4*	75	*3·2*	3	—	4	1,566	*2·3*
443,184	255,107		156,749		46,036		3,309	3,273	1,322,150	

lbirths; ‡ per 1,000 live births.
t or post

ng the pa mother's present and any previous husband. Abortions before 28 weeks of pregnancy are excluded.
s are not th were fewer than 10 stillbirths or deaths nor where the mother's age or parity was not stated.

THE EFFECT OF RELAXIN ON THE CONTRACTILITY OF THE HUMAN PREGNANT UTERUS

A Tocographic Study

BY

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RELAXIN

THE existence of Relaxin was first postulated by Hisaw in 1926 when he found that an extract of swine corpora lutea produced pelvic relaxation in oestrogen-treated guinea-pigs. Relaxation of pelvic ligaments and joints has since been demonstrated in other mammals, but the response has been shown to be the subject of species difference (Hall and Newton, 1947; Kliman *et al.*, 1953). The hormone has been shown to have other effects too. In oestrogen-treated spayed sows and heifers Relaxin is said to bring about marked cervical dilatation (Zarrow, Sikes and Nehen, 1954), while there is evidence that uterine contractility as a whole is inhibited in the guinea-pig (Felton, Frieden and Bryant, 1953), rat and mouse (Sawyer, Frieden and Martin, 1953).

Relaxin has been identified as a water-soluble polypeptide and purified preparations obtained from the ovaries of pregnant sows are now available for clinical assessment. The hormone has been found in the bloodstream of pregnant women and recent evidence suggests that its concentration increases to term and rapidly falls after parturition (Zarrow, Holstrom and Salhanick, 1955).

The results of animal experimentation with Relaxin have only been partially substantiated in the human subject and much work remains to be done before the functions of the hormone are clearly defined. Relaxation of pelvic joints is an accepted phenomenon of normal human pregnancy but it has yet to be shown that it is relaxin-induced. A number of observers have commented on the softness of the cervix in patients after relaxin therapy, but such an effect is difficult to assess accurately. Chief attention, so far as the human subject is concerned, has been focussed on the supposed effect of relaxin in inhibiting contractility of the human myometrium. There have, indeed, been several favourable reports on the ability of relaxin to suppress uterine contractions in premature labour (Abramson and Reid, 1955; Eichner *et al.*, 1956; Folsome *et al.*, 1956), but these studies have been based on clinical impression only. There appears to have been only one investigation, so far, in which the uterine contractions were recorded objectively (Kelly and Posse, 1956); in this the results seemed less impressive and no actual record of the uterine response was reproduced. We therefore determined to conduct an objective study of the effect of relaxin on the contractility of the intact pregnant human uterus by tocographic means.

This study was not designed to examine directly the effect of relaxin on premature labour because of the difficulty in selection of suitable cases and in accumulating a sufficient number in a relatively short space of time. Instead, the purpose of the investigation was simply to assess the effect, if any, of relaxin on the spontaneous contractions of late pregnancy and early labour at term.

Method

All the records of uterine contractility in this study were obtained by internal means using the Oxford tocograph (Embrey, 1958). In this method a small intra-uterine balloon, introduced between the membranes and the uterine wall above the presenting part, is hydraulically linked to a hydroflex bellows which forms the recording head of the instrument. In this way changes in intra-uterine pressure are accurately transmitted to the tocograph and graphic records of uterine motility obtained. The method has the advantage of convenience; sterilization of the recording unit is easy, the tocograph is always readily available for use and it requires little adjustment.

Tocographic records were obtained from 10 volunteer patients (5 primigravidae, 5 multigravidae) in whom surgical induction was indicated for some non-urgent condition (Table I). In some patients recording was begun at once; in others records were started after the onset of the first painful contractions of labour. Before recording, an intravenous drip infusion of glucose in distilled water was set up so that later injections could be made into the tubing of this apparatus without disturbance of the patient and the risk of psychological influences inhibiting uterine contractility. A second drip infusion set was then assembled with added relaxin, and at an appropriate moment, after a control period of recording, was connected to the first infusion apparatus to deliver measured amounts of the hormone intravenously over selected periods of time. The whole method was controlled by frequent pulse and blood pressure recordings and the foetal heart was auscultated at intervals. There were no obstetrical complications which could be ascribed to the method and each patient subsequently had an uncomplicated delivery of a live infant.

Relaxin Dosage

Although in the majority of published clinical reports the intramuscular route has been used, continuous intravenous infusion is physiologically preferable and was the method used in this study. The potency of relaxin is expressed in milligramme equivalents of a "standard" preparation of the hormone which has the activity of 150 guinea-pig units per milligramme (1 G.P.U. is the amount of hormone which induces relaxation of the symphysis pubis in oestrogen-primed guinea-pigs under standard conditions). The relaxin used in this study was supplied as "Releasin"* in 1 ml. ampoules of sterile aqueous solution, each phial containing 20 mg. (3,000 G.P.U.) relaxin standard.

* "Releasin" is the trade name of the brand of relaxin manufactured by William R. Warner & Co., Ltd. It was supplied to us through the courtesy of Dr. D. D. H. Craig.

Table I

Case No.	Type	Relaxin Dosage: Rate of Infusion (mg./min.)	Relaxin Dosage: Duration of Infusion (minutes)	Relaxin Dosage: Total Dose (mg.)	Length of Recording After Infusion (minutes)	Effect
PR 1 ..	Early labour	1·6	20	32	22	No effect.
PR 2 ..	Late pregnancy	2·0 / 4·0	10 / 15	80	6	No effect.
MR 3 ..	Early labour	7·1	14	100	11	No effect.
PR 4 ..	Late pregnancy	26·0	6	156	26	No significant effect.
PR 5 ..	Early labour	14·3	14	200	40	No significant effect. Nausea.
MR 6 ..	Early labour	12·5	16	200	25	No effect.
MR 7 ..	Late pregnancy	40·0	5	200	86	No effect.
PR 8 ..	Early labour	10·0	15	150	157	No effect. Rigor.
MR 9 ..	Late pregnancy	11·4	22	250	52	No effect. Vomiting.
MR 10 ..	Early labour	31·3	8	250	42	? Transient inhibition.

In the earlier investigations dosage was determined in the light of recommendations contained in the various published clinical reports; but in successive cases this dosage was gradually increased as experience allowed. It was thought at one stage that our preparation had deteriorated through storage, but this was not so as samples were returned to the manufacturers for assay and found to be fully potent by laboratory tests.

Results

In 9 out of the 10 cases relaxin had no significant effect on uterine contractility, either immediate or delayed (Figs. 1a, 1b). In the tenth case, with a very large dose of the hormone, there was transient inhibition (Fig. 1c) which was unsustained. As soon as the infusion was stopped normal uterine contractility recurred.

In general, there were few side effects. One patient complained of nausea, one of vomiting

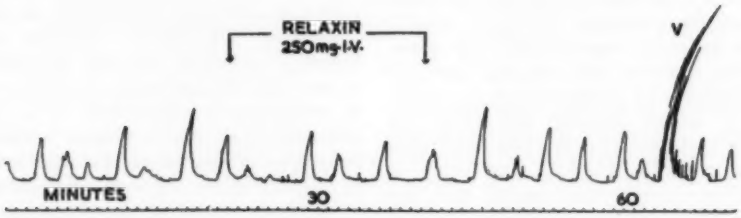

Fig. 1a

Relaxin by intravenous infusion. No demonstrable effect on uterine contractility in early labour. V = Vomiting.

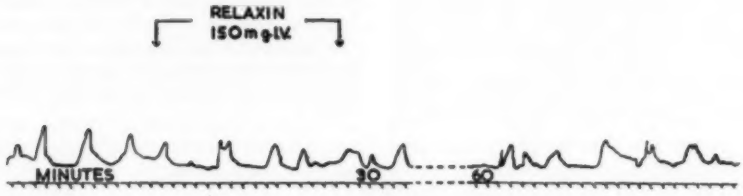

Fig. 1b

Relaxin by intravenous infusion. No demonstrable immediate or delayed effect on uterine contractility in late pregnancy.

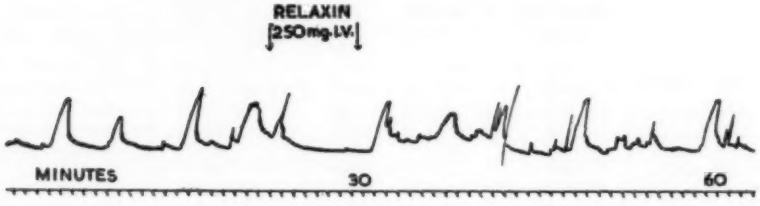

Fig. 1c

Relaxin by intravenous infusion. Possible transient inhibition of uterine contractility in early labour.

and a third patient had a slight rigor 50 minutes after withdrawal of the drug. No other symptoms were reported. Details of all investigations are given in Table I.

Discussion

The evidence that relaxin-containing preparations possess the desirable property of inhibiting uterine contractions in premature labour is derived partly from animal experiments and partly from studies of a purely clinical nature in the human subject. We have been unable, in the present work, to confirm tocographically in the human that relaxin has any significant action in suppressing uterine contractility in late pregnancy or early labour at term. It therefore seems most unlikely that the hormone could possess the ability to quell uterine contractions in cases of premature labour. Presumably, any beneficial effect of the hormone in premature labour has to be explained otherwise, and must be dependent on some characteristic not measured in this study. The nature of this property, however, is difficult to comprehend. It might be supposed that relaxin, by its presence, in some way prevents the conversion of the painless contractions of pregnancy which do not dilate the cervix into the painful contractions of labour which do so. But this explanation seems improbable if the claims that relaxin softens and dilates the cervix (Zarrow, Sikes and Nehen, 1954) are to be accepted.

The range of dosage used does not explain the apparent discrepancy between the results of this objective study and previous clinical reports. Abramson and Reid (1955) and Folsome *et al.* (1956), claim that 20–80 mg. of relaxin repeated 2–4 hourly by intramuscular injection stops premature labour, but in this present work relaxin in doses of up to 250 mg. by intravenous infusion has failed to alter the pattern of spontaneous uterine contractility. Any further increase in dosage would only exceed the limits of tolerance. It appears, therefore, that there is little evidence to support the claim that relaxin has an inhibitory effect on the motility of the intact human pregnant uterus. This opinion is supported by the recent work of McGaughey, Corey and Thornton (1958) who, in studies with the hormone, found no demonstrable effect on the spontaneous motility of isolated human myometrium *in vitro*.

It may well be that the hormone has other more important properties and its reported effect in softening the cervix holds promise of a sphere of usefulness in the induction of labour and in the treatment of protracted labour. But this property has not been investigated in the present study.

Summary

(1) In 10 volunteer patients the effect of relaxin on uterine motility in late pregnancy and early labour was recorded by internal tocography.

(2) No evidence was found to support the claim that relaxin has a significant inhibitory effect on the motility of the human pregnant uterus.

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DATA ON THE TIMING AND FREQUENCY DISTRIBUTION OF PAINS IN NORMAL LABOUR

BY

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IN the early stages of a study designed to improve obstetrical analgesia, it became necessary to observe the frequency of painful uterine contractions during the first stage. The data presented here are the result of observation of 15 labours from an original material of 47 labours, of which 32 were excluded because of the short period of observation (12 cases) or the presence of abnormal conditions (20). This policy of rigid exclusion was thought desirable in order that only normal subjects should be included. A total of 790 observations were made as detailed in Table I. These data are untouched excepting for adjustments to zero in 4 cases in accordance with principles explained by Yule and Kendall (1937). It will be noticed that they include only three multiparas—this arises from conditions at the particular hospital. In the two occipito-posterior cases rotation occurred spontaneously. With the sole exception of patient A the series *ended* in each case with the transition to the second stage.

The mean timings will be observed to have differed widely—from 1·78 minutes to 4·64 minutes, and it should be noted that the figures in the column to the left of the Table represent the deviation, in each case, from the patient's own mean timing, not that from the weighted mean entered at the foot of the Table. No adjustment to half minutes was made unless

TABLE I

Frequencies of Observation of Stated Time Intervals Between Pains During Labour. ±0 = 3 Minutes

Deviation from the individual patients mean timing = ±0 minutes	Patient	A	B	E	F	H	J	P	V	W	Ba	Ea	La	Ma	Na	Sa	
	Para	+	−	−	+	−	−	−	−	−	−	−	−	+	−	−	
	Presentation	·	LOA	·	LOA	LOA	ROA	LOA	·OA	LOA	LOP	LOA	LOA	LOL	LOP	LOL	Totals
	mins.																
−3							1					2			1		1
−2½			1	1			1					7			1		6
−2			1	2		2	8				2	8	1	1	4	1	23
−1½	2	5	6	1	2	14	1	2	2	7	8	6	3	4	8	4	57
−1	5	10	4	6	2	19	3	14	18	5	2	8	4	7	9	6	111
−½	8	4	5	3	3	29	27	20	14	2	8	9	4	5	8	4	149
±0	14	4	3	4	9	13	48	15	17	5	6	8	4	4	5	2	162
+½	13	1	5	3	8	10	30	10	8	6	8	11	3	2	3	2	117
+1	5	2	4	3	4	7	5	9	3	4	2	9	1	2	2	2	67
+1½	1	1	4	1	2	8	2	5	2	2	3	3		1	1	1	44
+2		1		1		4		3	2	2	2	2			1		19
+2½		1		1		3		2	1	2	2	1					13
+3		1	1			1			2	1							8
+3½			1			1			1						1		5
+4		2				2											4
+4½						2											2
+5		1															1
Totals		48	35	36	23	32	123	116	80	70	38	76	20	26	44	22	789
Means		1·78	3·01	3·42	1·93	3·74	3·41	2·61	2·84	2·93	2·74	3·81	3·75	2·15	4·64	2·84	

Weighted mean for the whole 789 observations = 3·07 minutes.

the difference amounted to 0·13 minute as observations, which were of pains not contractions, could not be made more accurately.

METHOD

The sensation of pain was indicated by the subject as soon as it began, and she was asked to say when the pain subsided. The duration of the pain was recorded with a stop watch, and the time interval from the beginning of one pain to the beginning of the next.

When the totals on the right of the Table are plotted against the deviations on the left we get the curve (strictly a frequency polygon) shown in the uppermost (thick) curve of Figure 1. This curve is interesting, since it can be reproduced from more elementary curves embodying known facts and reasonable assumptions.

The pains become more and more frequent as labour advances, so timing was only begun when it appeared that labour was not only established, but that the rhythm of uterine action had settled down. It was hoped in this way to avoid any trouble due to further acceleration of rhythm. An examination of the final data however shows this hope to have been misplaced. When the observations are split into two groups "early" and "late", by dividing each patient's record so that as many observations fall into the one class as into the other, it is found in most cases that the mean of the early group is greater than the mean of the late group. Taking the average of the means, without weighting, we

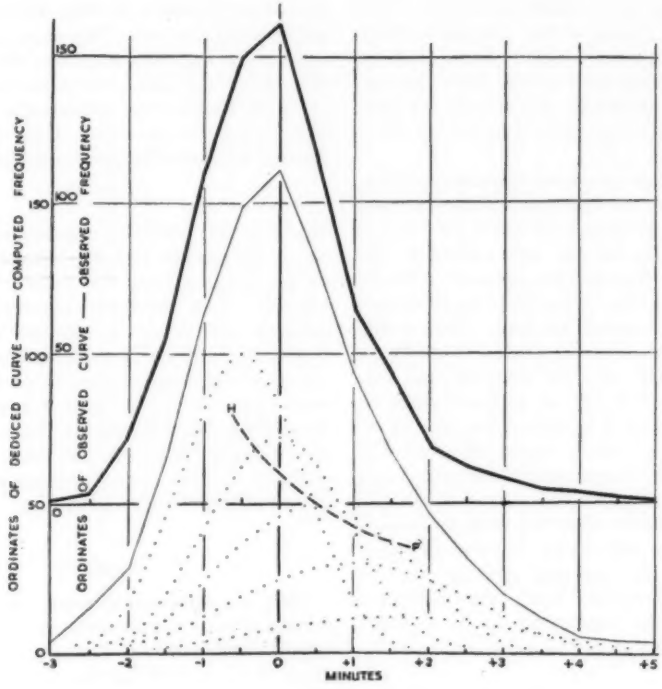

FIG. 1

Time intervals above or below 3 minutes.
(Zero of computed curve = + ½ minute.)

have—for the early groups 3·28 minutes and for the late groups 2·93 minutes, a difference of 0·35 minutes.

Figure 1 illustrates in the lower (lighter) curves the way in which the observed curve of frequency distribution may be thought to be generated. We may imagine that at any moment the chance of an interval exceeding the *mean for that moment* is equal to its chance of falling short of it. This might mean, for example, the temporary damming back of a nerve impulse by a dam whose breakdown point varies in random fashion. It might be thought that this would be easy to test by dividing the observations into smaller groups. This has been done in various ways, but it only serves to reveal something of the nature of a principle of indeterminacy. If the number of observations in the group is large the time occupied in registering them is such that some shortening of the interval is likely, while if the number is reduced the frequency distribution itself becomes meaningless; and no satisfactory combinations can be made because of the great disparity in the means. In these circumstances one can only accept the above assumption.

We may proceed to reason that since twice as many two-minute as four-minute intervals can be fitted into any period of time, the normal distribution curve which will represent our assumption for four-minute intervals must be doubled in height for two-minute intervals and correspondingly varied between. This would yield a set of curves whose modes would lie on the hyperbola HP. But the time interval falls with time, and if it did so in linear manner, from 4 minutes to 2 minutes then out of 40 observations (say) there would be about 16 between 3 and 4 minutes and 24 between 2 and 3 minutes, i.e., about means around $3\frac{1}{2}$ and $2\frac{1}{2}$ minutes respectively. Now the median division into two groups will throw 4 observations of average value $2\frac{1}{2}$ minutes among the 16 averaging $3\frac{1}{2}$ minutes. Thus, the difference between the group timings would be expected to be of the order

$$\frac{1}{20}(16\times 3\tfrac{1}{2})+(4\times 2\tfrac{1}{2})-\frac{1}{20}(20\times 2\tfrac{1}{2})=0\cdot 80 \text{ mins.}$$

But we have seen that this difference is actually 0·35 minutes. This would plainly be accounted for if there were a quicker transition from 4 minutes to 3 minutes than from 3 minutes to 2 minutes. There were no cases where this could be demonstrated owing to the great variability in timing, but it seems reasonable to anticipate it if the approach to 2 minutes is more or less exponential. I have assumed therefore that low summits in the distribution curves at the bottom of Figure 1 are to be depressed and high ones raised. By how much cannot be determined since it depends both on rate of recession of the mean from 4 minutes to 2 minutes and also on the particular mixture of observations actually present—in terms of the example adduced above, on how many $3\frac{1}{2}$s are mixed with the $2\frac{1}{2}$s anyhow. I have added 10 observations to the 2 minute set and deducted as many from the 4 minute with proportionate adjustment between. If these figures are reduced the downward sweep of the curve is less concave upwards, if increased more so; but even without any such correction some concavity remains.

So far we have no information as to dispersion, i.e., as to the value of the constant h, if the normal curves be represented by

$$y=ke^{-h^2\times^2}.$$

Nothing very definite appears from Table I but if we actually plot the individual spread of observations against the means a small correlation seems probable corresponding to 3 minutes spread at 2 minutes interval and 6 minutes spread at 4 minutes interval and the curves are drawn roughly to correspond. The lower main curve of Figure 1 is then obtained by adding the ordinates of the bottom curves and bringing them to the same scale as the curve of observations. The resemblance *in form* to the observed curve is striking.

Summary

Data are presented showing the frequency of painful uterine contractions in the first stage of normal human labour. It is concluded that while there is an overall pattern of some regularity this is not of such a degree as will enable accurate prediction of the time of onset of the pain to be made.

It is a pleasure to record my thanks to Professor J. C. McClure Browne for the invitation to work in his department and every encouragement; to the whole staff of the Maternity and the Biophysical departments at the Hammersmith Hospital for their kindness and help to a stranger and a layman; and lastly, with deep reverence, to the mothers themselves.

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UTERINE MOTILITY IN ANOVULATORY CYCLES

BY

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Two types of contraction can be recorded from the non-pregnant human uterus. In the normal menstrual cycle the characteristic pattern of uterine contractility is of rapid, feeble contractions or A waves in the first two weeks of the cycle and of very much larger and slower contractions or B waves in the last two weeks. This is the original description of Moir (1934, 1944). It is in direct conflict with the work of earlier German authors but is now generally accepted as correct (Henry and Browne, 1943). Moir's two contraction types are quite dissimilar. A waves show pressures of 0·1 to *c.* 2 mm. of mercury by the intra-uterine balloon method and recur at intervals of 15 to 60 seconds whereas B waves develop pressures of up to 100 mm. of mercury at intervals of 1 to 10 minutes. When B waves first appear they are superimposed on the existing A-wave activity (Garrett, 1956) and in the second half of the cycle it is usually possible to record both A waves and B waves simultaneously. As B waves never occur in the first two weeks of the menstrual cycle it may be postulated that their development depends on some phenomenon which only exists in the third and fourth weeks. It may be that the corpus luteum exerts a controlling influence. In this paper, this supposition is examined and records from normal and anovulatory cycles are studied.

METHOD

Records of uterine activity were obtained from 18 volunteer patients by the intra-uterine balloon method of Moir (1934). With customary antiseptic precautions the uterine cervix was exposed and a small, thick-walled, collapsed balloon mounted on a hollow sound was passed into the cavity of the uterus under direct vision without anaesthesia. When in place, the balloon was filled with water to an initial distending pressure of 15 mm. of mercury. As the maximum capacity of the balloon was designed not to exceed 2 ml., this initial distending pressure was balanced by the elasticity of the balloon rather than by the uterine wall itself. An approximation to isometric recording conditions was thus obtained. The balloon was then connected by water-filled pressure-tubing to a fine water tambour or mercury manometer recording on smoked paper.

The patients selected for examination were those in whom dilatation and curettage had been ordered on medical grounds and all were in the fourth week of the menstrual cycle. The recordings were taken the day before the operation. If ovulation were going to occur it would have done so by that time and with these arrangements the endometrium obtained would correspond in time as closely as possible to the time of the recording. The endometrium was examined histologically for secretory changes which indicate whether or not ovulation has taken place (Novak, 1952). In two cases the abdomen had to be opened and in these a corpus luteum was actually seen in the ovary.

RESULTS

In all patients showing evidence of ovulation (either secretory changes in the endometrium or a corpus luteum seen at laparotomy), the recording of uterine motility showed typical large, slow B waves as originally described in

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the second half of the normal menstrual cycle by Moir (1934, 1944). In 8 of the 12 patients showing B waves, A waves were recorded in and among the B waves. The absence of A waves from the other 4 cases may have been real. It was, however, more probably due to the difficulty of recording with a mercury manometer contractions of the order of 0·2 mm. of mercury (A waves) in the presence of other much larger contractions.

In each of the 6 patients having anovulatory cycles (as judged by the failure of the endometrium to show secretory changes), the uterine recording showed rapid, feeble A-wave activity only. These records are strictly comparable to those obtained from normal patients in the first two weeks of the menstrual cycle *before* ovulation has occurred.

Details of the cases studied are given in Table I and examples in Figure 1.

TABLE I

Case No.	Day of Cycle	A-wave Rate (rate/minute)	B-wave Rate (rate/hour)	Endometrial Phase or Other Evidence of Ovulation
1	21	1·5	—	Non-secretory.
2	22	2·1	—	Hypertrophic non-secretory.
3	24	3·0	—	Non-secretory.
4	26	2·9	—	Non-secretory.
5	27	3·7	—	Hypertrophic non-secretory.
6	28	2·9	—	Non-secretory.
7	22	3·4	36·0	Secretory.
8	23	2·6	37·0	Secretory.
9	23	—	10·3	Secretory.
10	25	—	9·5	Late secretory.
11	26	3·8	31·5	Early secretory.
12	26	1·9	18·8	Secretory.
13	26	2·8	12·0	Late secretory.
14	27	2·0	21·4	Late secretory.
15	27	3·0	66·7	Corpus luteum seen.
16	27	—	75·0	Late secretory.
17	27	—	33·3	Late secretory.
18	28	2·1	33·3	Corpus luteum seen.

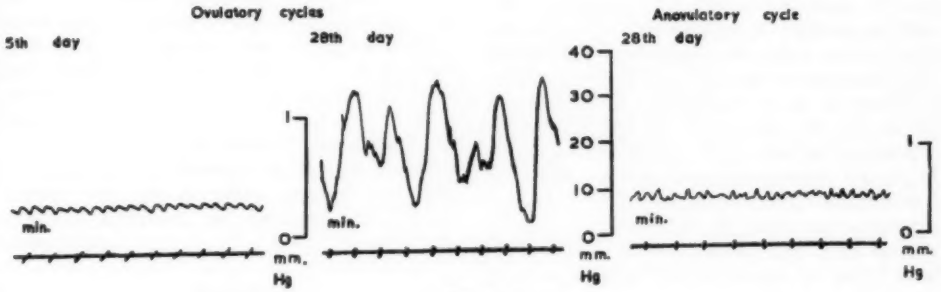

FIG. 1

Records of uterine motility in ovulatory and anovulatory cycles. In the first half of the menstrual cycle before ovulation has occurred, A waves are recorded. After ovulation, B waves are prominent. In anovulatory cycles B waves fail to develop and A waves only are recorded.

Conclusion

The large, slow B waves, which develop in the second half of ovulatory menstrual cycles, fail to appear in anovulatory cycles. As the secretory changes in the endometrium which accompany the development of B waves are known to be under the hormonal control of the corpus luteum (Sturgis and Meigs, 1936), it is quite likely that B waves are similarly governed.

Summary

(1) Records of uterine motility were obtained from 18 patients in the fourth week of the menstrual cycle.

(2) B waves were recorded in all ovulatory cycles but not in anovulatory cycles.

(3) Secretory changes in the endometrium were taken as evidence of ovulation.

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INACTIVATION OF OXYTOCIN BY PLASMA OF PREGNANT WOMEN

BY

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IN 1930, Fekete showed that the serum from pregnant women was able to inactivate the neurohypophyseal hormones, and this was confirmed by Werle, Hevelke and Buthmann, and by Werle and Kalvelage, in 1941. Since then it has been demonstrated that similar inactivation occurs with plasma (Page, 1946; Tyler, 1954; Werle and Semm, 1956; Dicker and Tyler, 1956; Carballo and Mendez-Bauer, 1957; Semm, 1957). According to Page (1946) and to Carballo and Mendez-Bauer (1957) the rate of inactivation of oxytocin by plasma from pregnant women increases as pregnancy advances and reaches its maximum towards the 36th to 38th week, after which it remains at the same level until delivery. From Tyler's (1954) investigation, however, it would appear that the rate at which plasma from pregnant women inactivates oxytocin is maximal at about the 26th week of pregnancy after which it decreases; and Dicker and Tyler (1956) have stated that plasma taken towards term usually failed to inactivate oxytocin.

The purpose of the present investigation was to re-examine the problem with a view to seeing whether the rate at which plasma inactivates oxytocin increases or decreases as labour approaches.

METHOD

Assays of oxytocic activity. The isolated rat uterus preparation (Holton, 1948) immersed in De Jalon, Bayo and De Jalon's (1945) Ringer-Tyrode solution was used, at a pH of 7·6–7·8, for oxytocic assays.

Blood sampling. Blood was taken from the antecubital vein with a siliconed syringe and collected in chilled siliconed glass centrifuge tubes containing about 5 mg. heparin. Plasma was separated by centrifugation and removed, avoiding the buffy coat.

Preparation of solutions. Ten units of oxytocin were added to 2·0 ml. plasma and diluted to 10 ml. with the modified Ringer-Tyrode solution. Following the addition of oxytocin, the pH fell to between 4·0–4·5, but was readjusted to 7·0 by addition of Na_2CO_3. The solution was divided into two samples, A and B, of 1·0 ml. and 9·0 ml. respectively. Sample A was plunged immediately into boiling water for 3 minutes; after cooling it was diluted 100 times, filtered and assayed. The amount of oxytocin activity estimated in this sample was taken as representing that in the plasma mixture before incubation, at time 0. The remaining 9·0 ml. of sample B were incubated at 37° C. for 10, 20 or 60 minutes, the solution being shaken constantly. At the end of the incubation period, 1·0 ml. of sample B was put into boiling water for 3 minutes and treated in the same way as sample A. Solutions were checked for their acidity before assaying, and adjusted to pH 7·0 if necessary.

Quantitative estimations. Addition of plasma to or changes in the ionic concentration of the solutions to be assayed may influence the

sensitivity of the isolated uterus (Bentley and Dicker, 1955). By ensuring a correct dilution and a constant pH, it was found, however, that it was possible to use a (2 and 2) dose assay (Schild, 1942). In a series of control experiments, it could be shown that plasma samples diluted 500 times (see above) with Ringer-Tyrode and incubated up to 2 hours at 37° C. had no stimulating effect on the rat uterus. Details about the validity of the assays and the limits of error will be given elsewhere. The volumes of known and unknown solutions added to the bath (capacity: 2·0 ml.) were 0·4 and 0·2 ml. for high and low doses respectively.

Statistics. Means are given with their standard error. The standard error of a percentage was calculated as $\sqrt{\frac{p \times q}{n}}$ where p is the percentage of oxytocic activity found and q the percentage of oxytocic activity which had been destroyed, p+q being equal to 100 (Bradford Hill, 1950). Regression equations and correlation coefficients were calculated according to Fisher (1944) and Mainland (1938). Allowance for the number of samples in any one series of estimations was made by determining the probability (P) of "t" or "r" from the tables of Fisher and Yates (1943).

Drug. Pitocin (Parke Davis and Co.) solution was used throughout.

Results

Plasma samples from 86 patients from University College Obstetric Hospital were investigated. The subjects were divided in 3 groups: (*a*) 52 pregnant women (duration of pregnancy from the 13th week after conception to term); (*b*) 14 patients in labour and (*c*) 20 postnatal cases. Plasma of 7 non-pregnant women and of 2 men were used as controls. As a rule, blood samples were taken once only from each subject, the choice of subjects being strictly randomized; it was taken twice, however, in 3 cases: at the 28th and 31st week; at the 14th and 40th week; and at the 37th and 41st week respectively; and in 4 postnatal cases during feeding of the child and between feeding hours.

No inactivation of oxytocin was observed either with plasma of non-pregnant women or men or from women whose pregnancy was shorter than 15 weeks. In all other cases, inactivation of oxytocin could be detected after 10 minutes incubation. Prolonging the duration of incubation increased the amount of oxytocin inactivated (Fig. 1).

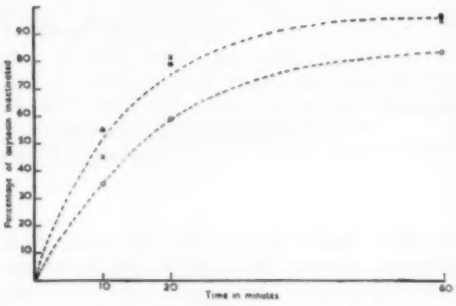

FIG. 1

Relation between oxytocin inactivation and duration of incubation. X: Plasma from a woman at her 40th week of pregnancy; ●: plasma from a woman in labour; O: plasma from a woman at 28th week. In each case, 2·0 ml. plasma were incubated with 10 U oxytocin at pH 7·0 and 37° C.

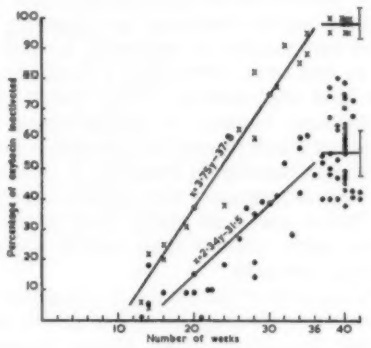

FIG. 2

Percentage of oxytocin inactivated by plasma from pregnant women at different periods of pregnancy. ●: after 10 minutes incubation; X: after 60 minutes incubation. In each case, 2·0 ml. plasma were incubated with 10 U oxytocin at pH 7·0 and 37° C. The vertical line | represents the standard error of the mean of percentages of oxytocin inactivation for values obtained between 37th and 42nd week of pregnancy.

From Figure 2 it will be seen that the amount of oxytocin inactivated by plasma increased regularly with the duration of pregnancy, from the 13th up to the 36th week after conception. The correlation coefficient between the percentage of oxytocin inactivated and the length of pregnancy was $r=+0{\cdot}903$, $SE=\pm0{\cdot}208$, $t<0{\cdot}001$ for 23 samples of plasma incubated for 10 minutes and $r=+0{\cdot}971$, $SE=\pm0{\cdot}271$, $t<0{\cdot}001$ for 15 samples incubated for 60 minutes. The difference between these coefficients was not statistically different ($t=0{\cdot}62$; $SE=\pm0{\cdot}36$). The regression equations for both correlation coefficients were $x=2{\cdot}34y-31{\cdot}5$ and $x=3{\cdot}75y-37{\cdot}8$, respectively (Fig. 2). From this it will be seen that whether the incubation lasted 10 or 60 minutes there was approximately a fivefold increase in the percentage of oxytocin inactivated from the 13th to the 36th week.

From the 37th week onwards up to the time of delivery there was no further increase in the rate of inactivation of the drug. The mean percentage of oxytocin inactivated after 10 minutes of incubation with plasma was 54·8 per cent$\pm$7·68 (41) (Fig. 2). The large standard error of nearly 15 per cent of the mean value may have been due to the fact that (*a*) results of inactivation by plasma of women at term or near it had been pooled with those of women already in labour; (*b*) all cases of labour had been treated together irrespective of whether they were normal or not. As a matter of fact 15 women were between the 37th and 40th week, and 15 between the 40th and 42nd week of pregnancy, while 14 were actually in labour. Of the last group, however, only 11 results of 10-minutes incubation are available. The mean percentage of oxytocin inactivated by plasma from pregnant women between the 37th and 40th week was 54 per cent$\pm$9·05 (15); this was not significantly different ($t=1{\cdot}339$; $P<0{\cdot}2>0{\cdot}1$) from the mean of 60 per cent$\pm$14·76 (11) observed for women in labour. Likewise the difference between the mean percentage of oxytocin inactivated in 6 cases of normal labour (58 per cent$\pm$10·15), was not significantly different ($t=1{\cdot}011$; $P<0{\cdot}4>0{\cdot}3$) from either that of 5 cases of uterine inertia (64 per cent$\pm$21·47) or that of 2 cases with severe symptoms of pre-eclampsia. It is then clear that in spite of the wide scatter of the results the titre of inactivation of plasma of pregnant women from the 37th week until delivery was much the same, and that during the last 4 weeks of pregnancy the plasma incubated with oxytocin required 10 minutes to inactivate just over 50 per cent of the added drug. These results are in close agreement with those of Carballo and Mendez-Bauer (1957).

After delivery, the percentage of oxytocin inactivated by plasma decreased progressively (Fig. 3); the regression equation of the line was

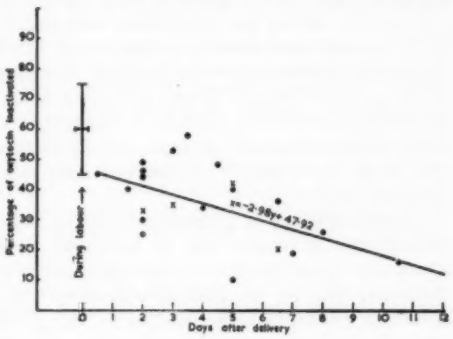

FIG. 3

Percentage of oxytocin inactivated by plasma after delivery. O: Plasma taken between feeding times; X: plasma taken during breast feeding. On the left: mean value with standard error of the percentage of oxytocin inactivated during labour.

$x=-2{\cdot}98y+47{\cdot}92$. Some inactivation of the drug was still observed after 60 minutes of incubation with plasma taken 11 and 12¼ days after delivery. Plasma taken 6 weeks after confinement had no effect on the oxytocic activity of the drug, even when the incubation had been prolonged up to 2 hours. No difference in the amount of oxytocin inactivated by plasma was found whether blood had been taken during the period of breast feeding or between feeding times, in 4 cases 2, 3, 5 and 6 days after delivery.

DISCUSSION

The present investigation shows that blood plasma from pregnant women inactivates oxy-

tocin *in vitro*, and that the amount of oxytocin inactivated in a given time increases with the duration of pregnancy, from about the 13th to the 36th week after conception. This confirms previous findings by Page (1946), Carballo and Mendez-Bauer (1957) and Caldeyro-Barcia and Poseiro (1958). The power of inactivation of plasma from a woman in labour is such that 2·0 ml. of plasma incubated *in vitro* with oxytocin inactivated more than 5 units of the drug in 10 minutes. According to Heller and Zaimis (1949), however, the whole posterior lobe of adult man contains about 14 units of oxytocin only. The existence of such a mechanism *in vivo* during late pregnancy and during labour would mean that "a woman is protected maximally against a natural oxytocic hormone at the onset of labour" (Page, 1946) but would invalidate the view that oxytocin is "the principal factor which increases uterine activity during pre-labour or labour" (Caldeyro-Barcia and Poseiro, 1958).

It must however be emphasized that no valid quantitative deduction can be extended from the *in vitro* experiments to *in vivo* circumstances. Assuming that we are dealing with an enzymic system, it will be remembered that the rate of an enzymic process depends primarily on the concentrations of both the enzyme and its substrate, and that, according to Michaelis's theory, with a fixed concentration of an enzyme the reaction velocity increases with increasing substrate concentration. Thus with very low concentration of the substrate—here, the oxytocin—the reaction velocity may be infinitesimally small. This might explain why intravenous infusions of as little as 1·0 mU oxytocin per minute produce marked uterine contractions in the pregnant human (Page, 1943; Theobald *et al.*, 1948; Theobald, Kelsey and Muirhead, 1956; Nixon and Smyth, 1958; Caldeyro-Barcia and Poseiro, 1958), as small amounts of the hormone could reach the target organ practically unaffected by the circulating enzyme.

The question then is: has this *in vitro* reaction any significance in obstetrics? Page (1946) suggested that it might be used as a qualitative test for early pregnancy but it would appear that no inactivation of oxytocin can be detected when plasma of women pregnant for less than 13 weeks is used. Dicker and Tyler (1956) had suggested that the reaction might help to diagnose cases of uterine inertia, and hence help in their treatment. This too has now to be rejected: plasma samples of women suffering from uterine inertia, whether tested at the end of the pregnancy or during labour, showed no difference in efficiency to inactivate added oxytocin.

According to Carballo and Mendez-Bauer (1957) the property of inactivating oxytocin is due to an enzyme which seems to be produced by the placenta (Page, 1946; Hawker, 1956); this enzyme would appear in the blood only during pregnancy and only in those species with placenta haemochorialis, i.e., in human and monkey. Indeed neither Page (1946) nor Tyler (1954) could find signs of oxytocin inactivation with plasma of pregnant rats, rabbits, guinea-pigs or bitches. It is interesting to note that Sawyer (1954) could demonstrate in *in vitro* experiments a "striking increase in oxytocinase activity in uterine muscle during pregnancy" in the rat.

It would seem therefore that the mechanism of inactivation of oxytocin by plasma of pregnant women is still very incompletely understood.

Summary

(1) Blood was taken from men and non-pregnant women, from pregnant women at different stages of their pregnancy, and from women during labour and after delivery. Plasma samples of 2·0 ml. were incubated with 10 U oxytocin at pH 7·0, and 37° C. for 10, 20 and 60 minutes and the rate of oxytocin inactivation determined.

(2) No inactivation of oxytocin was observed after incubation with plasma from men, non-pregnant women or pregnant women whose pregnancy was shorter than 13 weeks.

(3) Plasma from women pregnant for more than 13 weeks always inactivated oxytocin. The amount of oxytocin inactivated increased regularly with the duration of pregnancy up to the 36th week, after which no further increase took place. From the 37th week until delivery, it could be shown that 2·0 ml. plasma incubated

with 10 U oxytocin inactivated about 50 per cent of the drug in 10 minutes.

(4) There was no relation between rate of oxytocin inactivation and the occurrence of uterine inertia.

(5) After delivery, the rate at which plasma inactivates oxytocin decreases slowly. Some degree of oxytocin inactivation could still be observed after incubation with blood plasma taken from women 10 days after delivery.

The authors wish to thank Professor W. C. W. Nixon for allowing this investigation to be carried out on patients in University College Obstetric Hospital.

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INTRAVENOUS PROTOVERATRINE IN THE PREVENTION AND MANAGEMENT OF ECLAMPSIA

BY

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THE management of eclampsia, imminent or overt, is essentially the same. Kellar (1955) states "the obstetrician must prevent, at all costs, the onset of convulsions and he has to try to return the patient to a state of moderate or mild pre-eclampsia".

While there is fairly general acceptance of these ideals of treatment in broad outline, there is no unanimity of opinion as to how this may best be accomplished. The diversity of management is mirrored in recent literature. The most widely accepted of the recent methods advocated are basal Avertin (Dewar and Morris, 1947), intravenous sodium thiopentone (Browne, 1950), magnesium sulphate (Eastman, 1956), Chlorpromazine (Mitra and Das Guptas, 1957), Hexamethonium (Townsend, 1955) and Hydralazine (Sherman and Riva, 1954).

F. J. Browne (1946), Sophian (1953), Meilman (1953a, b), Kellar (1955) and most other authorities agree that the disease results in generalized arteriolar spasm and attribute many or most of the serious sequelae, immediate or remote, to this vasoconstriction.

In this hospital, we believe protoveratrine has many advantages and approaches the ideals of management outlined above. There have, however, been few published reports of its use in recent literature, although Meilman (1953b), Krupp *et al.* (1954, 1956) and Morris (1955) have made favourable reports.

This report attempts to demonstrate the usefulness of intravenous protoveratrine in a series of 25 patients whose pregnancy was complicated by a marked rise in blood pressure. Four of these patients had eclampsia.

Veratrum derivatives have been used for many years in the management of hypertension in pregnancy with varying degrees of popularity. Two explanations for the extreme views for and against these derivatives were the confusion which existed between pharmacological and toxic effects and the difficulty in preparing extracts which gave predictable and reproducible results. Highly purified preparations are now available and a better understanding of the pharmacology has resulted from the work of Krayer *et al.* (1943, 1944), Krayer and Acheson (1946), Stutzman and Maison (1950), Maison and Stutzman (1951), as well as other workers.

Bryant (1935), Bryant and Fleming (1940), Garber *et al.* (1950), Assali (1950), Baird and Assali (1951) have advocated and defended the use of Veratrum extracts and Sophian (1953), Stern and Burnett (1954) consider them valuable therapeutic agents. McCall (1954) successfully used combined Veratrum and Apresoline therapy for the management of severe hypertension in pregnancy.

Protoveratrine is a purified crystalline ester of protoverine which is derived from the root of *Veratrum album*. It consists of two isomorphously crystallizing alkaloids protoveratrine A and B which vary only in one hydroxy group—Nash and Brooker (1953) and Stoll and Subeck (1953).

Krayer *et al.* (1944), Hoobler and Corley (1950a, b), Hoobler *et al.* (1952), Meilman and Krayer (1949, 1950, 1952) and Meilman (1952) studied the pharmacological responses and effects of this preparation and Rothlin and Cerletti (1954) reviewed its pharmacology.

The main pharmacological actions of protoveratrine are:

(*i*) A hypotensive response, which is the result of generalized arteriolar dilatation, and differs from that caused by ganglionic blocking agents and anti-adrenergic drugs. The mechanism is thought to be partly central and partly reflex. Stimulation of receptors in the region of the coronary arteries, particularly the left coronary artery, is said to be most important. Stimuli pass to the vagal and vasomotor centres *via* afferent vagal fibres—Bezold-Jarisch reflex. Pressor and chemoreceptors in the carotid sinus are said to play a minor role.

(*ii*) Bradycardia which may augment but it is not essential for the hypotensive response. The mechanism of the bradycardia is one of strong central vagal stimulation. The bradycardia may be abolished by atropine.

(*iii*) A digitalis-like effect on the failing heart.

Material

Recently protoveratrine has been the drug mainly used in this hospital for the in-patient management of raised blood pressure in pregnancy, the route of administration depending on the severity of the hypertension; oral therapy for mild, intramuscular for moderate and intravenous for severe hypertension. Following the initial rapid reduction in blood pressure with intravenous protoveratrine we have endeavoured to maintain the blood pressure at or just above normotensive levels with intramuscular or oral administration.

In this series of 25 cases protoveratrine was administered initially by the intravenous route in an attempt to control the hypertension. Subsequently, it was administered intramuscularly in 21 cases and again intravenously in 4 cases.

The cases in this series were made up of 4 cases of eclampsia; 16 cases of pre-eclampsia; 4 cases of essential hypertension with superimposed pre-eclampsia and 1 case of chronic pyelonephritis.

The drug was administered ante-partum in 17 cases and post-partum in 8 cases and in many of these cases it was used after magnesium sulphate and paraldehyde had been unsuccessful.

The preparation of protoveratrine, P.V.S. 295 ("Puroverine" Sandoz), contained protoveratrine A and B in the proportion of two parts protoveratrine A to one part protoveratrine B and was supplied in ampoules containing 0·1 mg. per ml.

Method

The technique used for intravenous protoveratrine injection was as follows: A solution was prepared containing 0·1 mg. (1 ampoule) in 10 ml. of distilled water or 5 per cent glucose in distilled water. This solution, containing 0·01 mg. protoveratrine per ml., was injected at a rate of slightly more than 1 ml. per minute until a fall of about 30 mm. of mercury systolic and about 25 mm. of mercury diastolic was recorded. The injection was then stopped temporarily and progress observed. The blood pressure usually continued to fall and the maximum response was obtained in most cases within 20 to 60 minutes. If the hypotensive response was not obtained within a reasonable time, a further injection of the drug was given at the same rate until a satisfactory response was obtained.

It was necessary to have a team of at least two to carry out this procedure satisfactorily—one injecting, the other recording the blood pressure and pulse rate. These were recorded continuously during injection and for a quarter of an hour following a maximum response. Thereafter they were recorded at 5-minute intervals for half an hour. For the remainder of the duration of therapy, blood pressure and pulse rate were recorded at ¼, ½, 1 and 2 hourly intervals. After the initial satisfactory response further doses of the drug were given intramuscularly with the object of maintaining blood pressure levels at 120–140/70–90 mm. of

TABLE I

		Initial Effective Fall in Blood Pressure	Before	After	Dose	Time of Maximum Response
					(mg.)	
Eclampsia:						
1	Ante-partum	Yes	210/140	130/90	0·3	50 minutes
2	Ante-partum	Yes	200/115	160/85	0·3	60 minutes
3	Ante-partum	Yes	170/120	130/80	0·23	30 minutes
4	Post-partum	Yes	160/115	110/80	0·2	30 minutes
Pre-eclampsia:						
5	Ante-partum	Yes	195/135	120/80	0·2	35 minutes
6	Ante-partum	Yes	170/110	120/80	0·15	30 minutes
7	Ante-partum	Yes	175/110	160/90	0·3	35 minutes
8	Ante-partum	Yes	170/130	120/70	0·5	50 minutes
9	Ante-partum	Yes	190/130	125/95	0·2	45 minutes
10	Ante-partum	No	210/135	190/135	0·75	No effective response in 3¼ hours
11	Ante-partum	Yes	190/130	140/95	0·33	35 minutes
12	Ante-partum	Yes	175/120	80/55	0·2	75 minutes
13	Ante-partum	Yes	180/120	110/80	0·13	20 minutes
14	Ante-partum	Yes	195/125	130/85	0·25	31 minutes
15	Post-partum	Yes	180/140	120/80	0·15	35 minutes
16	Post-partum	Yes	220/115	140/75	0·2	60 minutes
17	Post-partum	Yes	190/120	125/75	0·4	90 minutes
18	Post-partum	Yes	210/160	160/100	0·2	70 minutes
19	Post-partum	Yes	185/120	150/100	0·21	75 minutes
20	Post-partum	Yes	215/140	130/90	0·75	3 hours
Essential Hypertension with Superimposed Pre-eclampsia:						
21	Ante-partum	Yes	215/140	140/90	0·4	44 minutes
22	Ante-partum	Yes	180/140	135/90	0·2	90 minutes
23	Ante-partum	Yes	185/145	110/70	0·4	75 minutes
24	Post-partum	Yes	240/140	130/90	0·2	22 minutes
Chronic Pyelonephritis:						
25	Ante-partum	Yes	200/150	140/100	0·17	45 minutes

mercury. These intramuscular injections were given at varying intervals depending on the response and the dose was adjusted accordingly.

RESULTS

Effective Hypotensive Response

An effective initial hypotensive response was obtained in 24 cases. These responses are summarized in Table I.

The dose required to obtain these responses varied between 0·13 mg. and 0·75 mg. The time for the maximum response varied between 22 minutes and 3 hours.

Two types of effective response were encountered:

(I) *Immediate*—In 16 cases, after a short latent period, the blood pressure fell progressively. The maximum fall was recorded 5–30 minutes after completion of the dose. This type of response is illustrated in Figure 1 (Case 14).

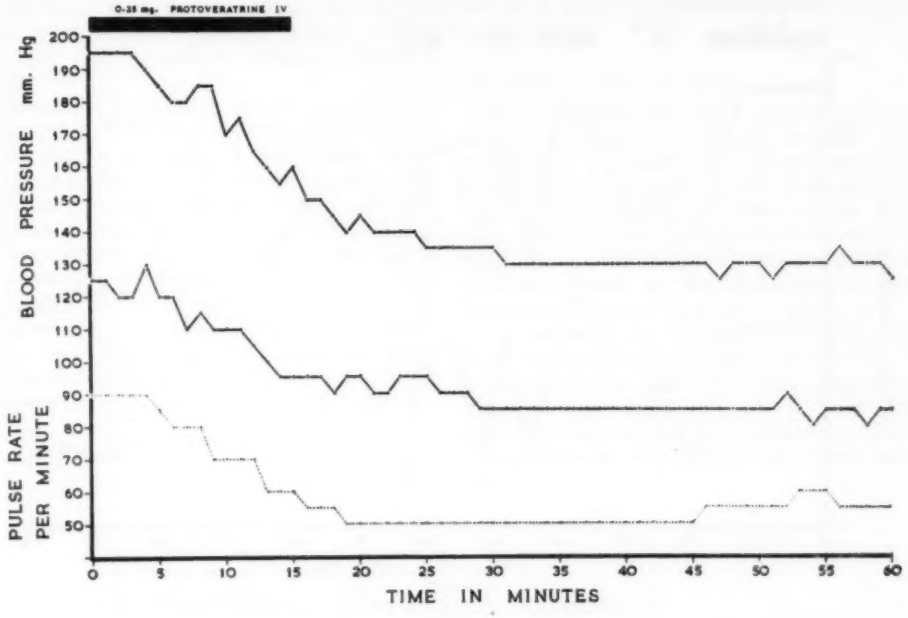

FIG. 1

Case 14. Initial immediate hypotensive response to I.V. protoveratrine.

The dose range in this group varied between 0·13 mg. and 0·5 mg. In 15 cases the maximum response was obtained 20–50 minutes from the commencement of administration and in the 16th case in 1 hour.

(II) *Delayed*—The delayed response was of three types:

(*a*) In 6 cases the fall in blood pressure followed the same pattern but was much more gradual than that of the first group. The maximum fall was recorded 40–72 minutes after the completion of the dose.

The dose range in this group varied between 0·2 mg. and 0·4 mg. and the maximum response obtained 1–1½ hours after the commencement of intravenous administration.

(*b*) In 1 case the fall in blood pressure was interrupted by a series of peaks which, in the early stages, were as high as or higher than those recorded at the onset of treatment. Each of these peaks required a further injection of the drug. The maximum fall was finally recorded 1 hour after the completion of the dose and 3 hours after the commencement of treatment. The total dose was 0·75 mg. Since compiling this series we have observed a similar initial response which is illustrated in Figure 2. This type of response was also provoked in Case 3 when the blood pressure rose for the second time subsequent to the initial control. Again the dose was large, discontinuous and the final response delayed. In these three instances the response, once obtained, was sustained for 24–48 hours.

(*c*) In 1 case (Case 12) the initial hypotensive response was delayed and excessive and was obtained 75 minutes after the commencement of treatment. The dose was small, 0·2 mg., and the final fall occurred after the blood pressure

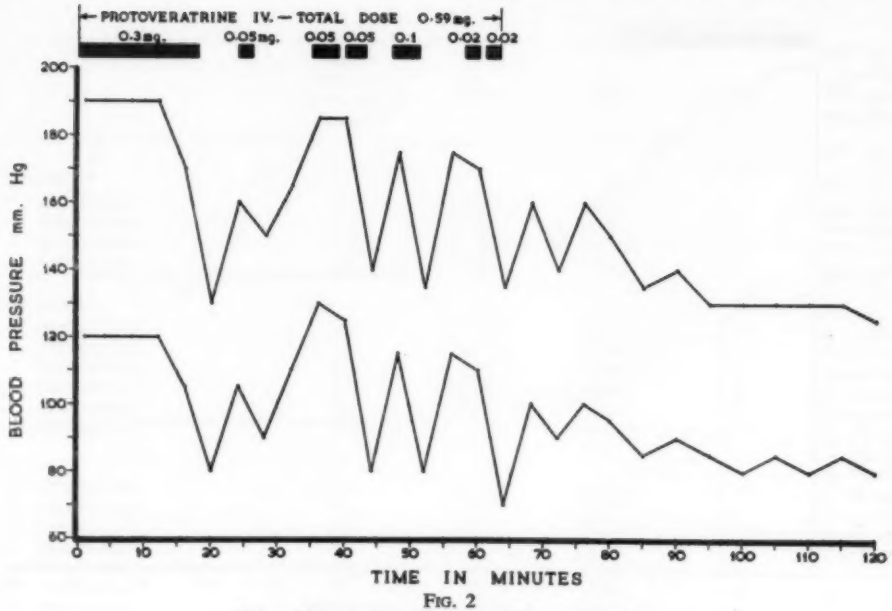

FIG. 2
Delayed hypotensive response to I.V. protoveratrine.

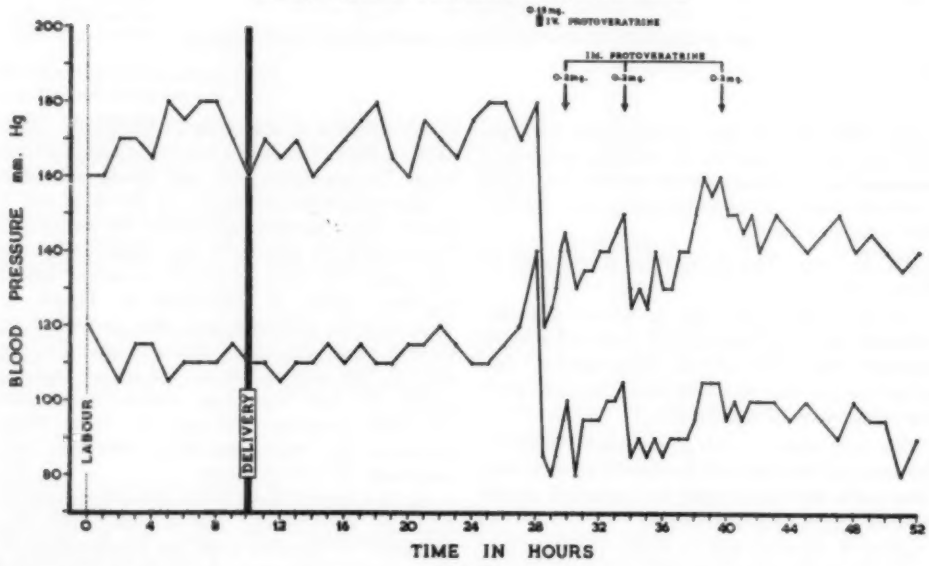

FIG. 3
Case 15. Control of hypertension with I.V. protoveratrine following failure of magnesium sulphate and paraldehyde.

appeared to have been stabilized for half an hour. This response resembled in some respects the first type of delayed response described above.

Successful hypotensive control was achieved when other drugs had been unsuccessful in a large number of cases. A satisfactory hypotensive response to protoveratrine intravenously after unsuccessful treatment with magnesium sulphate is demonstrated in Figure 3 (Case 15). In the majority of cases in which a hypotensive response was obtained this was followed after a variable period by significant rise in blood pressure. With 2 exceptions the subsequent levels were lower than those recorded before treatment. These subsequent rises in blood pressure are illustrated in Figures 5, 6 and 7.

Failed Response

The one failure occurred in Case 10 whose history is summarized below and is illustrated in Figure 4.

Subsequent Control of Blood Pressure

In 20 cases, after the initial satisfactory hypotensive response, the blood pressure was successfully controlled by intramuscular injection of the drug. In 1 case (Case 22) this was accomplished for a further 8 days prior to the induction of labour without evidence of resistance to the drug. The subsequent blood pressure control by intramuscular administration is illustrated in Figure 5 (Case 5).

To maintain the hypotensive response the drug was again administered intravenously in 4 cases. In one three subsequent intravenous injections were required. In one of these cases (Case 23) the response to a subsequent intravenous injection was excessive and is discussed below.

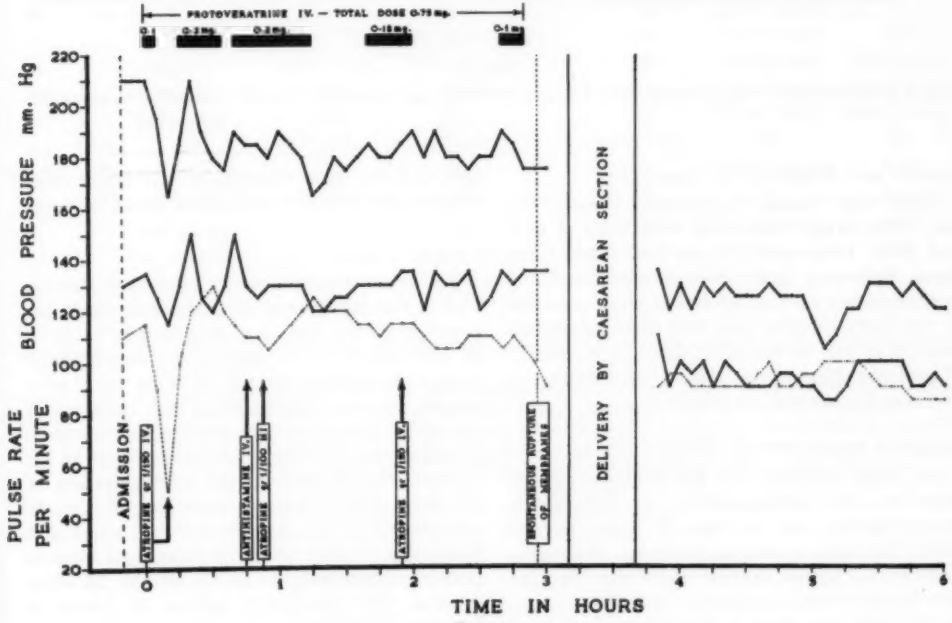

FIG. 4

Case 10. Failed response to I.V. protoveratrine.

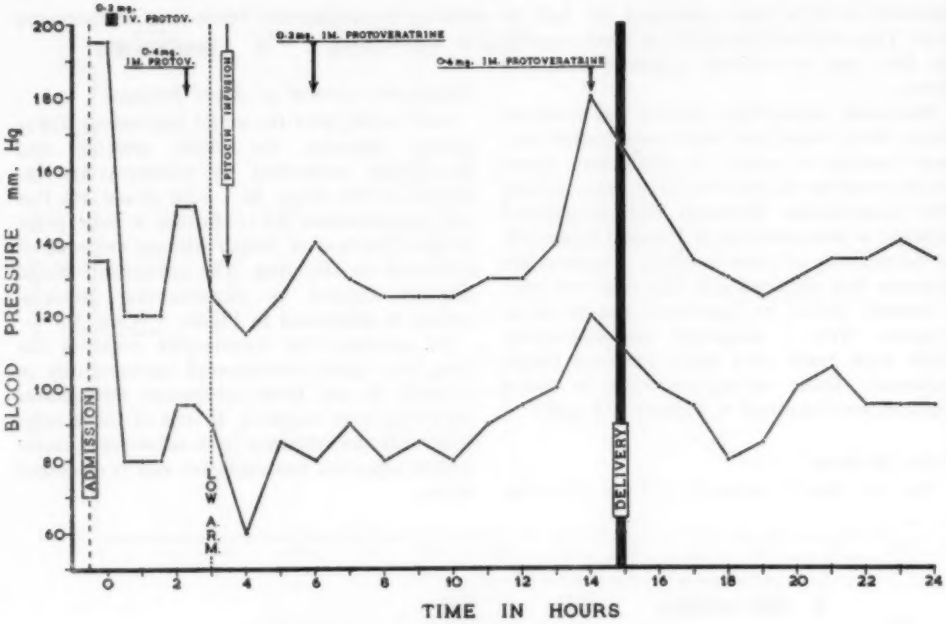

FIG. 5

Case 5. Initial control of hypertension with I.V. protoveratrine and subsequent control with I.M. protoveratrine.

Control and Prevention of Convulsions

There were 4 cases of eclampsia. Prior to the use of the drug, 1 case had fitted once, 1 case had fitted twice and 2 cases had fitted three times. Following intravenous administration of protoveratrine no further convulsions occurred in the cases of eclampsia nor did convulsions develop in any of the other cases. The efficacy of protoveratrine in controlling the convulsions in Case 3 is shown in Figure 6.

Relief of Headache and Blurred Vision

In 5 cases headache was the leading symptom prior to the administration of intravenous protoveratrine and in one of these blurred vision was also a leading symptom. Following intravenous administration there was prompt alleviation of these symptoms in 4 of the cases. In the fifth case there is no record of whether improvement occurred but it is assumed that this was so. In a subsequent case rapid relief of headache followed administration of the drug.

Urinary Output

The urinary output (where known) preceding, and in the subsequent 48 hours following, the use of protoveratrine is summarized in Table II. In one case (Case 1) oliguria and subsequently anuria developed. In the 6 cases who were known to be oliguric before the intravenous administration there was marked improvement in urinary output to a level above 500 ml. in the 24 hours subsequent to the administration of the drug. Although the urinary output prior to administration was not known in 7 cases it is likely that at least some of these were oliguric before administration. In all of the 24 cases diuresis was established within 36 hours of intravenous administration. The rate of diminution of oedema paralleled the diuretic response.

TABLE II

Case	Total Urinary Output			Protein		
	In ml. per 24 Hours Unless Otherwise Stated			At Onset of Treatment with Proto-veratrine	After	
	Before	1st 24 Hours	2nd 24 Hours		At 24 Hours	At 48 Hours
1 ..	360 (12 hours)	240	Nil	Solid	—	—
2 ..	Not known	1,920	3.030	9/10	1/4	Heavy cloud
3 ..	240 (14 hours)	1,625	3,460	Solid	1/4	Heavy cloud
4 ..	120 (7 hours)	2,220	Satisfactory	1/2	Nil	Nil
5 ..	Not known	720	4,090	Solid	1/2	Faint cloud
6 ..	1,430	1,950	Satisfactory	1/2	Heavy cloud	Nil
7 ..	Satisfactory	1,050	Satisfactory	1/2	Heavy cloud	Faint cloud
8 ..	750 (12 hours)	1,442	1,812	Heavy cloud	Nil	Nil
9 ..	Satisfactory	1,320	Satisfactory	1/6	Faint cloud	Faint cloud
10 ..	Not known	1,890	4,650	Solid	Heavy cloud	Heavy cloud
11 ..	180 (9 hours)	1,280	4,060	7/8	Heavy cloud	Faint cloud
12 ..	Not known	540	1,370	Solid	1/4	Faint cloud
13 ..	Not known	1,140	1,710	1/2	Heavy cloud	Heavy cloud
14 ..	90 (5 hours)	863	2,130	Solid	1/4	Faint cloud
15 ..	360	1,740	4,560	Solid	Heavy cloud	Nil
16 ..	1,200	3,150	Satisfactory	1/6	Heavy cloud	Nil
17 ..	1,140	Satisfactory	Satisfactory	1/8	Heavy cloud	Faint cloud
18 ..	1,260	1,440	1,680	1/4	Heavy cloud	Heavy cloud
19 ..	Satisfactory	1,290	1,780	3/4	Heavy cloud	Heavy cloud
20 ..	720	2,520	Satisfactory	Heavy cloud	Nil	Nil
21 ..	210 (6 hours)	1,140	3,190	1/3	Heavy cloud	Nil
22 ..	Not known	1,740	3,240	1/2	Nil	Nil
23 ..	Not known	1,050	3,280	Solid	Faint cloud	Nil
24 ..	180 (6 hours)	Satisfactory	Satisfactory	1/3	Faint cloud	Nil
25 ..	370	780	2,070	Solid	1/8	Heavy cloud

Satisfactory: The exact measurements are not known but there was never concern that the urinary output was below normal limits.

Proteinuria: Routine testing of the urine in this hospital is performed by the boiling test—the urine is first filtered and then acidified. A test-tube of the urine is then boiled, and allowed to stand for an hour. The amount of protein relative to the volume of urine is then estimated. An attempt is made for uniformity in these estimations. We have endeavoured to correlate the absolute values of proteinuria in g./litre with those estimated by the boiling test. The approximate values are as follows:

Solid	:	15–17 g./litre
7/8–9/10	:	12–14 g./litre
2/3–3/4	:	8–11 g./litre
1/2	:	6 g./litre
1/4–1/3	:	2·3–2·6 g./litre
1/6–1/8	:	1·2 g./litre
1/10	:	1·0 g./litre
Heavy cloud	:	0·7–0·9 g./litre
Faint cloud	:	0·4–0·6 g./litre

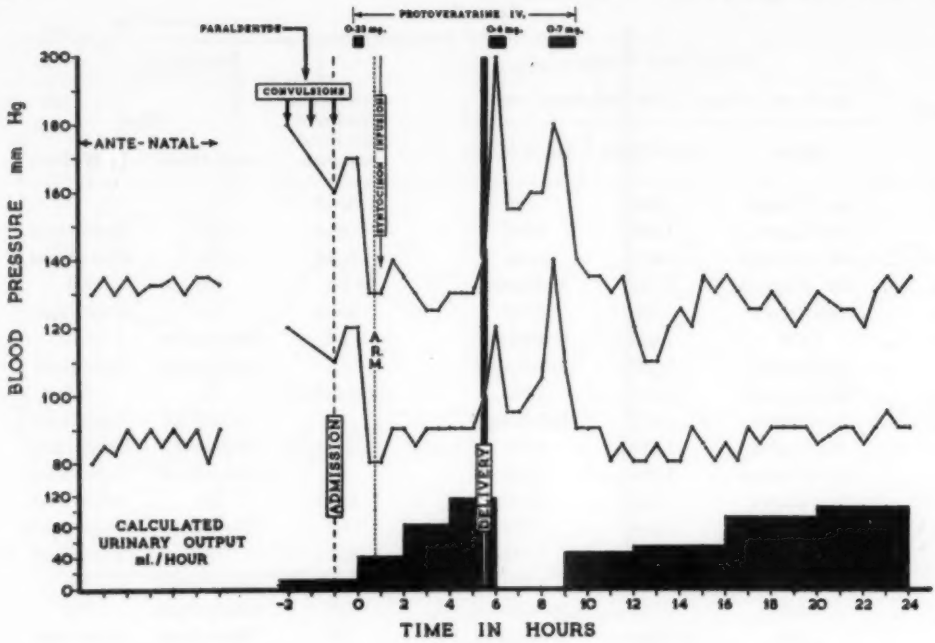

FIG. 6

Case 3. (*a*) Control of convulsions with I.V. protoveratrine; (*b*) control of hypertension with repeated I.V. protoveratrine; (*c*) diuretic response following control of hypertension.

(Figure 6 illustrates the diuretic effect which results from lowering the blood pressure.)

Proteinuria

The degree of proteinuria at the onset of the administration and 24 and 48 hours later is summarized in Table II. With 1 exception (Case 1) there was an appreciable diminution of the degree of proteinuria in all cases.

Maternal Mortality

There was one maternal death in this series (Case 1). This death was not attributed to protoveratrine and the cause of death is discussed more fully below.

Foetal Mortality

One pregnancy (Case 25) was terminated by abdominal hysterotomy at 22-weeks gestation.

Intravenous protoveratrine was administered ante-partum to 16 cases in which pregnancy had reached 28-weeks gestation. There were 12 living children (1 case of twins), 2 stillbirths and 3 neonatal deaths. These results are shown in Table III and the deaths discussed below.

Onset of Labour and Method of Delivery

These are summarized in Table III.

Onset of labour. The onset of labour was spontaneous in 5 cases, induced by artificial rupture of the membranes in 4 cases, by artificial rupture of the membranes followed by Pitocin or Syntocinon infusion in 5 cases; by repeated Pitocin infusion in 1 case and Caesarean section before the onset of labour in 1 case.

Method of delivery. Spontaneous delivery occurred in 5 cases; low forceps extraction was performed in 8 cases and Caesarean section in 3 cases.

TABLE III

Case	Gestation in Weeks	Onset of Labour	Method of Delivery	Birth Weight		Result
				Pounds	Ounces	
1	29	Spontaneous	Spontaneous	2 (1,027 g.)	5	Stillbirth Autopsy—Anoxia.
2	30	Pitocin infusion	Spontaneous	2 (1,058 g.)	6	Stillbirth. Autopsy—extreme maceration.
3	36	Low A.R.M. Syntocinon infusion	Low forceps	5 (2,365 g.)	6	Alive and well.
5	36	Low A.R.M.	Low forceps	4 (1,991 g.)	8	Alive and well.
6	42	Spontaneous	Low forceps	6 (2,800 g.)	6	Alive and well.
7	39	Low A.R.M.	Caesarean section	6 (2,768 g.)	5	Alive and well.
8	38	Low A.R.M.	Low forceps	7 (3,070 g.)	1	Alive and well.
9	39	Low A.R.M.	Low forceps	7 (3,391 g.)	11	Alive and well.
10	42	Not in labour	Caesarean section	6 (2,613 g.)	0	Neonatal death—12 hours. Autopsy—anoxia.
11	38	Low A.R.M.	Low forceps	5 (2,365 g.)	6	Alive and well.
12	35	Spontaneous	Caesarean section	4 (1,929 g.) 4 (1,866 g.)	6 4	Twins alive and well.
13	37	Spontaneous	Precipitate	4 (2,053 g.)	10	Neonatal death—1 hour. Autopsy—subarachnoid and subdural haemorrhage.
14	40	Low A.R.M.	Low forceps	7 (3,236 g.)	6	Alive and well.
21	34	Low A.R.M. Syntocinon infusion	Spontaneous	4 (1,742 g.)	0	Alive and well.
22	35	High A.R.M. Pitocin infusion	Low forceps	3 (1,307 g.)	0	Alive and well.
23	32	Spontaneous	Spontaneous	4 (1,898 g.)	5	Neonatal death—2 weeks. Autopsy—bilateral hydronephroses.
25	22		Hysterotomy			

Bradycardia

Significant bradycardia (a fall in pulse rate of more than 30 per minute) occurred in 21 cases. The typical hypotensive-bradycardia effect is shown in Figure 1. Although a fall of pulse rate to about 50 per minute was commonly observed, in only 1 case did the pulse rate fall significantly below this level. When the pulse had fallen to about 50 per minute atropine was administered with a prompt restoration to the pre-existing rate. With the exception of Case 10, this did not appear to have any significant effect on the blood pressure.

Side Effects

Side effects occurred in 8 cases and were in all cases rapidly controlled; the pattern of side effects varied in different cases. One case exhibited 5 and another 3 different side effects. In 2 cases they were transient and untreated.

Nausea and vomiting was the most common side effect and occurred in 5 cases. Three of these required no treatment. In those 2 cases who vomited more than once control of the vomiting was achieved by chlorpromazine.

Excessive hypotension occurred in 2 cases. In Case 12 the hypotension was mild and delayed

as the blood pressure had been stabilized for half an hour preceding the sudden fall. It was rapidly corrected with 15 mg. intravenous Methedrine. In Case 23 profound hypotension to 50/30 followed the second intravenous administration of protoveratrine to a patient who had already received 0·8 mg. of the drug in the preceding 6 hours. This fall was fairly rapidly corrected with a large dose of intravenous Methedrine; the blood pressure was restored to 130/90 in 40 minutes. See Figure 7. The patient was unaware of any untoward effects nor was there any subsequent evidence of foetal distress.

Cardiac arrhythmias. Irregularities of the pulse occurred in 3 cases and were rapidly corrected by the administration of intravenous atropine. In 1 case the irregularity was shown to be pulsus bigeminus with occasional ventricular extrasystoles and, in this instance, followed intramuscular administration.

Retrosternal burning occurred in 1 case and was transient and untreated.

Gross swelling of salivary glands and peri-orbital oedema occurred in 1 case. Its onset was sudden and first noticed about 45 minutes after the commencement of protoveratrine administration. It was associated with excessive salivation and rhinorrhoea. The salivary adenopathy resembled that seen in severe mumps and the peri-orbital oedema was similar in appearance to angio-neurotic oedema. Resolution followed within 40 minutes of intravenous antihistamine administration.

Excessive salivation occurred in 1 case concurrently with the adenopathy and peri-orbital oedema described above. The duration of this was probably shortened by the atropine given to control the irregularity of the pulse.

Rhinorrhoea occurred in Case 10 simultaneously with the two preceding side effects. We have since observed rhinorrhoea in our

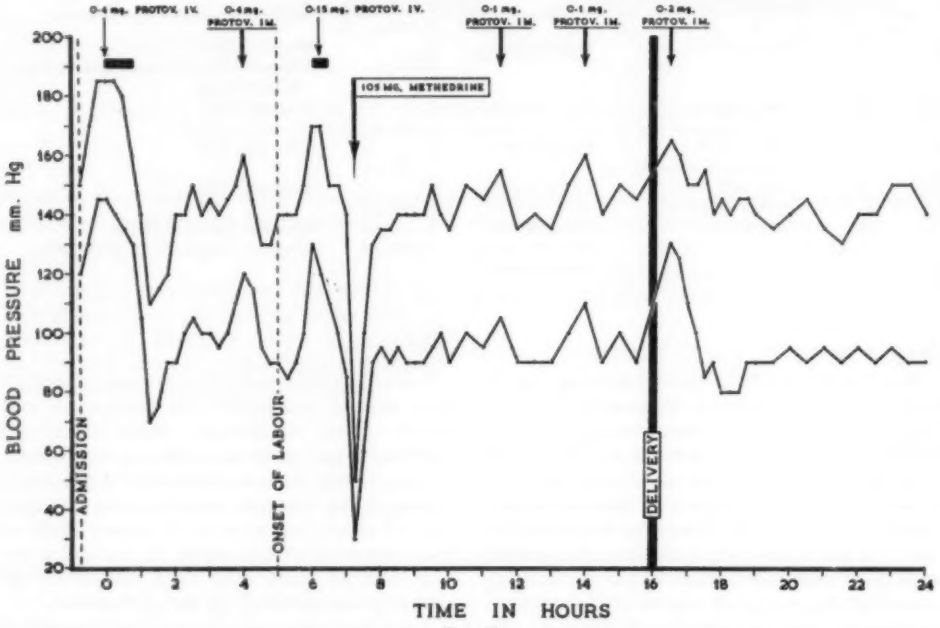

FIG. 7

Case 23. Excessive response to I.V. protoveratrine corrected with methedrine.

most recent case. The prompt alleviation following antihistamine would support the supposition that this was a hypersensitivity reaction.

The following brief case notes are relevant to the text and discussion.

Case 1

Ante-partum eclampsia. Non-booked, primigravida, 22. Uneventful pregnancy until 29th week when admitted to nearby suburban hospital with headache, bright vaginal bleeding, abdominal pain, gross oedema, blood pressure 210/140, a tense tender uterus and a trace of proteinuria. Despite heavy sedation with morphine, magnesium sulphate and paraldehyde, 3 convulsions occurred. Transferred to this hospital after the third convulsion. On admission—semi-conscious, grossly oedematous, tense uterus enlarged to 36-weeks gestation, draining blood-stained liquor, blood pressure 210/140, urine solid protein, and a bedside test revealed mild fibrinogen depletion. (She was transfused with 1,000 ml. of whole blood which controlled the coagulation defect.) Blood pressure was initially controlled with intravenous protoveratrine, and later by a further intramuscular injection. No further protoveratrine was given. She was delivered spontaneously 8½ hours after admission. No further convulsions occurred. During the 12 hours prior to her admission to this hospital, she passed 360 ml. of urine. In the first 24 hours in this hospital she passed 240 ml. of urine. Thereafter her daily urinary output was 0, 0, 60, 225, 180, 330, 225, 480, 600, 760, 915, 840, 880, 1,170 ml. During this period she was treated with a modified Bull's regime, but, despite apparently good electrolyte control, she died early on the fifteenth day with a blood urea of over 800 mg. per cent. During the first 36 hours of the puerperium, her blood pressure remained between 130–160/95–115, but rose to 200–220/115–120 on the third day, remaining at this level for 5 days when it gradually fell and was normotensive for the 4 days preceding death. During the first 5 days of the puerperium she was given a total of 1,250 ml. of packed red cells in four separate infusions for the correction of the anaemia. Autopsy revealed macroscopic bilateral cortical necrosis and histopathological examination revealed tubular necrosis.

Case 3

Ante-partum eclampsia. Non-booked, primigravida, 30. Pregnancy uneventful until the 36th week. She reported to her local doctor for routine antenatal visit. Her only complaint was that she had been unable to pass urine since going to bed the night before. She was grossly oedematous and her blood pressure was 180/120. During examination she had her first convulsion and was given paraldehyde and transferred to this hospital. During transit she had a further convulsion and the third convulsion occurred immediately on admission. Blood pressure 170/120, grossly oedematous, urine contained solid protein on boiling. She was given intravenous protoveratrine with a satisfactory response. Labour induced by low artificial rupture of the membranes and syntocinon infusion. Blood pressure remained stable until immediately after delivery (the labour lasted 5 hours) when it rose to 200/120. Intravenous protoveratrine was again repeated. Subsequently the blood pressure again rose to 180/140. During administration of the third intravenous dose the pulse became irregular. This was rapidly corrected by intravenous atropine. This patient received the largest intravenous dose given in this series. Following the final intravenous injection, blood pressure remained stable at 120–135/80–95 for a further 24 hours before intramuscular protoveratrine was necessary. During the puerperium blood pressure was controlled with intramuscular protoveratrine. This patient had no sedation apart from pethidine, 200 mg. during labour. She remained conscious and symptom-free throughout the treatment. On discharge—blood pressure 135–150/85–90, intermittent mild proteinuria. The control of convulsion and diuretic effect resulting from the hypotensive response is demonstrated in Figure 6.

Case 5

Pre-eclampsia. Non-booked, primigravida, 24. Admitted in 36th week after 3-weeks unsuccessful treatment for pre-eclampsia in another hospital. On admission—gross oedema, blood pressure 195/135, solid proteinuria. Initial control of blood pressure with intravenous and subsequent control with intramuscular protoveratrine. Labour, which was induced by low artificial rupture of the membranes and Pitocin infusion, lasted about 12 hours. Follow-up—blood pressure 140/80, proteinuria a cloud on occasions. Figure 5 demonstrates the initial response to intravenous protoveratrine and the subsequent control with intramuscular protoveratrine.

Case 10

Pre-eclampsia. Booked, gravida-2, 26. Uneventful pregnancy until early 42nd week. Admitted with weight gain of 14 pounds in a week, gross oedema, blood pressure 210/130, solid proteinuria. Ten minutes after the commencement of the first injection of intravenous protoveratrine the blood pressure had fallen to 165/115 and the pulse rate to 50 per minute. Following intravenous atropine the pulse rate increased to 120 per minute and the blood pressure quickly rose to 210/150. Administration of protoveratrine was continued and was followed by vomiting for which chlorpromazine was given. Acute and gross swelling of the submandibular and parotid glands with periorbital tissue and excessive salivation and rhinorrhoea developed 45 minutes after therapy commenced and about 10 minutes later irregularity of the pulse was noticed. She was given antihistamine intravenously and atropine subcutaneously with rapid correction of the irregularity of the pulse and alleviation of the salivary adenopathy within 30–40 minutes. Protoveratrine administration was continued without a hypotensive response. A further irregularity of the pulse occurred and was controlled with atropine

intravenously. Despite a further injection of intravenous protoveratrine, there was no effective hypotensive response. Three hours after the onset of therapy the membranes ruptured spontaneously with the passage of heavily meconium-stained liquor and the foetal heart sounds became slow (60–80) and irregular. Caesarean section was performed but the foetus died 12 hours later. Immediately following Caesarean section, blood pressure was 135/115. It soon fell to 130/90 and remained at 130–140/90–100 for the next 48 hours. Follow-up—normotensive, no proteinuria. The failed hypotensive response is illustrated in Figure 4.

Case 12

Pre-eclampsia. Non-booked, primigravida, aged 19. Admitted 35th week after unsuccessful treatment at another hospital. Gross oedema, blood pressure 175/120, twin pregnancy, solid proteinuria. Initial response to intravenous protoveratrine with fall in blood pressure to 135/100 within half an hour. During this time membranes ruptured spontaneously and labour commenced. Blood pressure remained at about 130–140/90–95 for a further half hour but 15 minutes later it had fallen to 80/55 with a fall in pulse rate to 30 per minute. Prompt restoration of blood pressure to 125/80 followed intravenous methedrine, 15 mg., and the pulse rate rose to 100 per minute following intravenous atropine. Caesarean section was performed 3 hours after the hypotensive episode for foetal distress in one twin (foetal heart sounds 60 per minute and irregular). Subsequent blood pressure control with intramuscular protoveratrine. Follow-up—blood pressure 110–130/75–90, intermittent mild proteinuria.

Case 14

Pre-eclampsia. Booked, primigravida, 20. Uneventful pregnancy until 40th week. Presented with headache, oliguria, gross oedema, blood pressure 195/125 and solid proteinuria. Initial control of blood pressure and prompt relief of headache with intravenous protoveratrine. However, the patient complained of nausea and retrosternal burning for a 15-minute period during the initial administration. This was not treated and did not recur. Labour induced by low artificial rupture of the membranes 2 hours later. Delivered by low forceps extraction under local anaesthesia after 16-hour labour during which blood pressure was controlled with intramuscular protoveratrine. This patient was given no sedation apart from pethidine, 300 mg., during labour and morphine, gr. 1/6, 1½ hours after delivery when she complained of pain at the episiotomy site. On discharge —blood pressure 130–140/80–90, no proteinuria. The initial response to intravenous protoveratrine is illustrated in Figure 1.

Case 15

Pre-eclampsia. Booked, primigravida, 23. Pregnancy uneventful. Admitted in labour 42nd week with nausea, severe headache, gross oedema, blood pressure 160/120, solid proteinuria. During 10-hour labour, heavily sedated with paraldehyde and magnesium sulphate. Delivered by low forceps extraction. Post-partum, despite further sedation with the above drugs, pentobarbitone and pethidine, blood pressure remained high. The oliguria persisted and the patient complained of severe headache. During the first 24 hours of treatment she was given in all 45 ml. paraldehyde, 35 ml. of 50 per cent magnesium sulphate intramuscularly, gr. 3, pentobarbitone and 300 mg. pethidine. Eighteen hours postpartum blood pressure had risen to 180/140, urine contained solid protein and she had passed only 360 ml. of urine in the preceding 24 hours. Blood pressure control with intravenous protoveratrine initially, subsequently with intramuscular protoveratrine. Headache improved and urinary output increased. On discharge—blood pressure 110–120/70–80, persistent trace of proteinuria. She has since had an uncomplicated pregnancy and labour. Figure 3 demonstrates the hypotensive response to protoveratrine following failure of magnesium sulphate and paraldehyde.

Case 23

Essential hypertension with superimposed pre-eclampsia. Non-booked, gravida-6, 33. Pregnancy said to be uneventful until 30th week when she developed oedema without other signs. By 32nd week blood pressure had risen to 160/120 and oedema increased. Admitted with vomiting, severe headache, gross oedema, blood pressure 150/120 and solid proteinuria. Blood pressure rose in next hour to 185/145. Given intravenous protoveratrine with a satisfactory response and relief of headache and vomiting. Some 3 hours later blood pressure again rose to 160/120 and responded to intramuscular protoveratrine. An hour later, following spontaneous onset of labour, the blood pressure rose to 175/130 and intravenous protoveratrine was administered. The expected response was obtained within three-quarters of an hour but blood pressure fell precipitately 15 minutes later to 50/30. Restored to 130/90 in 40 minutes with large doses of methedrine. Thereafter blood pressure controlled with smaller intramuscular doses. She was delivered spontaneously 8½ hours after the excessive hypotensive episode. There was no evidence of foetal distress at any stage, either during or subsequent to the hypotensive episode. On discharge—blood pressure 145–160/95–110, spasmodic mild proteinuria. The subsequent excessive hypotensive response is illustrated in Figure 7.

Discussion

As long as the aetiology of eclampsia remains unknown, the most profitable line of treatment would appear to be that directed towards the relief of generalized vasoconstriction which is such a prominent feature of this disease and which can lead to such serious sequelae. While agreeing that protoveratrine is not a specific therapeutic agent, we believe that it is a most

useful drug and will, in the majority of cases, fulfil these aims and restore the patient to a state approaching physiological normality. Following control of vasoconstriction the pregnancy may, if necessary, be prolonged for a limited period and the labour and delivery conducted under more favourable circumstances. (In one reported case the pregnancy was prolonged for a further 7 weeks.)

The hypotensive response is an index of the relief of vasospasm and is reflected in an improved circulation in the brain, heart, kidney and uterus. This in turn leads to a decrease in many of the complications responsible for the foetal and maternal mortality in this disease.

McCall (1949) demonstrated markedly increased cerebral vascular resistance in this disease and Byrom (1954) showed convincing evidence that convulsions are the result of intense vasoconstriction. Crumpton *et al.* (1951) have shown that following intravenous protoveratrine there is an increase in cerebral blood flow, the result of release of vascular spasm. The efficacy of protoveratrine is supported by the fact that no further convulsions occurred in the 4 cases of eclampsia once protoveratrine was administered, nor did convulsions occur in any of the other cases in this series. While it is impossible to state how many of these cases would have progressed to eclampsia, it is felt likely that some would have done so. In the 3 cases of eclampsia given minimal sedation before protoveratrine, the patients remained conscious and co-operative throughout subsequent treatment, which in 2 cases included induction and conduct of labour. Marked improvement in headache and blurred vision is further evidence of the release of cerebral vasoconstriction and the subsequent improvement of cerebral circulation and oxygen utilization.

Left ventricular failure and pulmonary oedema were not encountered in this series but Currens *et al.* (1954) have demonstrated the use of protoveratrine in the prevention and control of this complication in hypertensive cardiovascular disease.

Most workers have demonstrated a transient oliguria associated with the maximum hypotensive response. This had been attributed to a period of adaption by the kidney to the lowered pressure or an increased production of antidiuretic hormone as the result of the fall in blood pressure. It usually follows an abrupt fall in blood pressure as a result of too rapid administration. It may be avoided by a slow injection which will, in most instances, produce a gradual reduction in blood pressure. Kaeser (1954) made a similar observation. Our results demonstrate the improvement in urinary output and diminution in the degree of proteinuria which usually accompany administration of the drug in this manner. An improvement occurred in all patients known to be oliguric before beginning treatment and may be attributed in part to improved renal blood flow consequent upon vasodilatation. The association between improvement in the urinary output and the fall in blood pressure is amplified by reference to Figure 6.

Morris (1955) has demonstrated a sustained improvement in effective uterine blood flow following protoveratrine administration. This must benefit the foetus, providing impairment of placental function has not progressed to an irreparable degree. In addition, protoveratrine, unlike hexamethonium, does not predispose the foetus to ileus nor pneumonia. Apart from these directly beneficial effects, the foetal wastage should be reduced because, with such control of hypertension, the necessity to resort to Caesarean section as a means of delivery will be reduced. It is generally accepted that the foetal mortality rate due to atelectasis and hyaline membrane disease is higher in premature infants delivered abdominally (Donald, 1954). In this series, certainly small, there were no neonatal deaths from this cause among the premature infants delivered vaginally.

Delayed response. It is significant that the initial maximum response to intravenous protoveratrine may be delayed. A delayed response would appear to be, in the majority of cases, a manifestation of mild drug resistance which may develop quickly. In this series, 5 of the 7 cases in whom this response was provoked were already receiving the drug by other routes. Further support is given by the fact that this type of response was subsequently displayed in Case 3 after an initial immediate response and also in 2 of our more recent cases who were receiving

the drug intramuscularly. Although this series is small statistical analysis indicates that those patients already receiving the drug are much more likely to display this response.

There is a marked similarity between the first type of delayed response and that following intramuscular administration in that the maximum fall is gradual and progressive but delayed.

Intense vasospasm as well as some degree of drug resistance would appear to provoke the second type of delayed response which, once obtained, was sustained and prolonged for over 24 hours in all 4 cases. There is no obvious explanation for such a sustained response. It is important to continue administration in these cases until the desired response is obtained, even though large doses are necessary and the procedure is time-consuming. It is felt that some reported cases of failed response to protoveratrine may have followed this pattern.

Failed response. In some ways this case resembled that illustrated in Figure 2 in which the response was delayed for 3 hours, and it could possibly be argued that it represented a variant of the second type of delayed response described above. It is difficult, however, not to attribute part of the delayed fall in blood pressure to the delivery. The repeated atropine administration, given initially for the bradycardia and subsequently for irregularities of the pulse, may have played a part in this failed response. Hoobler, Corley and Kabza (1952) and other workers have reported some cases in which a rise in blood pressure followed abolition of the bradycardia by atropine. Failure of continued and adequate dosage was thought to be more important.

Maternal mortality. The death in this series (Case 1) resulted from renal failure due to renal cortical necrosis. Although it is difficult not to incriminate protoveratrine, this death is not attributed to the drug. Firstly, there is no known toxic effect on the kidneys; secondly, our own work and that of other workers shows that renal function improves rather than deteriorates with the use of the drug. Meilman (1953b) reported a case of eclampsia who was anuric; the urinary output improved following protoveratrine and this improvement was maintained with continued use of the drug. Thirdly, it seems unlikely that hypotension could be blamed, as this patient's blood pressure at no stage fell below 130/90; fourthly, the association of renal cortical necrosis and severe accidental haemorrhage with a high mortality rate, particularly in the 23–31 week gestation period (Sheehan and Moore, 1952) would make the development of this complication not unexpected, irrespective of protoveratrine administration; finally, there have been no deaths reported which were attributed to this drug.

Foetal mortality. Protoveratrine was not considered to play a part in 3 foetal deaths; the first, an intra-uterine death before admission; the second, a congenital malformation and the third, intracranial haemorrhage following a precipitate second stage.

The other 2 foetal deaths require discussion but neither was attributed to protoveratrine. The stillbirth in Case 2 occurred some 15 hours after the control of the eclampsia. The association of intra-uterine death due to placental inadequacy in eclampsia in the 30th week is well known and it is felt that death probably resulted from this. In Case 10 death resulted from the anoxia which was first noted ante-partum, and was probably due to placental insufficiency, the result of postmaturity and severe pre-eclampsia. Inhaled meconium resulted in a slow and incomplete response to resuscitation which further depressed the respiratory centres. The intra-uterine anoxia may, to some extent, have been alleviated if protoveratrine had effectively relieved vasoconstriction and improved the uterine blood flow.

Side effects will inevitably be associated with extensive use of protoveratrine but are not an indication to discontinue the drug. A proportion of the side effects are transient and require no treatment. Those due to over-dosage should be avoided by careful administration. The potentially dangerous ones and those involving discomfort to the patient respond rapidly to specific measures. *Excessive hypotension* is potentially the most dangerous side effect. There is no obvious explanation for the excessive hypotension in Case 12 unless it was a variant of one of the delayed responses described above. In Case 23 it was probably due to over-dosage. It is interesting that neither of these patients

was aware of anything untoward during the hypotensive episode nor did the hypotension appear to interfere with renal function or the welfare of the foetus. However, in both, it was of short duration and rapidly corrected. Meilman considers that hypotension induced by protoveratrine—by virtue of the generalized vasodilatation—is not as dangerous as hypotension from those causes associated with intense vasoconstriction in the unaffected areas. Its occurrence in this series stresses the necessity for careful administration and the ready availability of pressor agents. *Salivary gland enlargement* has been observed by us in only one case in the large number of patients to whom we have administered protoveratrine by any route and we have been unable to find a report of a similar case. A much more slowly developing salivary adenopathy, the result of iodide sensitization, is well known but in this case there was no history of previous veratrum administration. It seems most likely that this side action was due to drug idiosyncrasy or hypersensitivity, and this supposition would be supported by the prompt response to the antihistaminic.

Conclusions

Intravenous protoveratrine is an effective hypotensive agent for use in the pregnant or puerperal woman. The drug is safe providing certain precautions are observed, but its initial administration should not be attempted except in a hospital where trained staff is available. The patient must be under constant observation during administration and for some time after the presumed maximum hypotensive response is obtained. As a result of the control of vasoconstriction there is an improvement in the cerebral, renal and uterine circulation with amelioration of the signs and symptoms and prevention of serious sequelae. With return of the patient to a normotensive, or near normotensive state, obstetric procedures may be undertaken under more favourable circumstances.

Summary

(1) This paper presents the experience gained in the administration of intravenous protoveratrine to 25 patients whose blood pressure was raised to high levels in pregnancy, labour or the puerperium. Four of these patients had had eclamptic convulsions.

(2) The method of administration is described in some detail and certain precautions are emphasized.

(3) An initial effective hypotensive response was obtained in 24 cases. Different patterns of response are described. It is suggested that the delayed response in some cases may have been due to mild drug resistance and that failed responses should not be attributed to the drug unless adequate and continued dosage had been given.

(4) The control of convulsions in the 4 cases of eclampsia was prompt, and it is suggested that the onset of convulsions was prevented in some of the other cases. Dramatic relief of headache in 4 cases, scotoma in 1 case and vomiting in 1 case are attributed to the relief of vasospasm.

(5) Providing the blood pressure is lowered gradually, protoveratrine does not appear to depress the urinary output nor to interfere with the onset of a diuresis.

(6) Side effects occurred in one-third of the cases but were not troublesome and were rapidly controlled. With due precaution, many may be avoided. Parotid and submandibular adenopathy is reported, it is thought for the first time.

(7) It is felt the protoveratrine could not be blamed for the maternal death from renal cortical necrosis, nor for the foetal deaths.

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TREATMENT OF IRON DEFICIENCY ANAEMIA

A Comparison of Methods, with Particular Reference to Chelated Iron and Intramuscular Iron

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THIS paper reports a therapeutic comparison of two organic iron salts, Ferrous gluconate and Ferrous succinate with chelated iron in the form of iron aminoates, and iron given intramuscularly. We know of no other work in which these recent methods of iron therapy are compared, and have attempted to replace clinical impressions with careful clinical investigation.

We have, furthermore, in these series, doubled the dose of both oral and intramuscular iron that was used in a previous investigation, (Cope, Gillhespy and Richardson, 1956) to determine whether or not it is possible to increase the rate of improvement by increasing the daily dose beyond that which we have in the past considered adequate.

DESIGN OF THE CLINICAL TRIAL

Ferrous succinate was chosen as we have obtained a satisfactory daily haemoglobin rise in previous clinical trials, with a relatively small dose, in hypochromic anaemia resulting from various causes (Gillhespy, 1955; Cope *et al.*, 1956).

Ferrous gluconate was used as a control with ferrous succinate, in order to see if a small change in the organic radicle made a material difference to tolerance and therapeutic response, and to test the claims for the virtues of these relatively similar salts.

"Imferon" was used for intramuscular injection, as it is the only iron preparation available for this form of therapy. We have previously reported satisfactory results with this preparation, and we wished (*a*) to test whether the *rate* of therapeutic response, which is of particular importance in antenatal cases, could be increased by increasing the daily dose, and (*b*) to compare it with a chelated iron preparation and with organic iron salts in a similarly increased dosage.

Iron aminoates was chosen as it was the first satisfactory chelated iron to become available to us in sufficient quantity. Chelation is the binding of metallic cations by chelating agents, a term derived from the Greek word "chele" meaning a claw. These chelating or complex-forming agents are organic chemicals, which, when expressed in chemical symbols, appear to hold metallic cations with a claw-like grip, and it is this power to seize and sequester metallic cations so that they cease to exhibit their natural characteristic properties, which gives these agents their importance in nature, in industry—and more recently in pharmacology.

The avidity of such a complex for metallic cations is known as the stability constant. If this is high, as in, for instance, the avidity of porphyrin for iron, no further exchange with the same metal can take place. The amino-acids, peptides and proteins have, however, a lower

stability constant. These, when acting as chelating agents, grip the metallic cations tightly, but not so tightly as to preclude exchange.

Chelation is a possible factor in the variability of absorption of iron from the intestinal tract. Certain foods such as spinach reduce absorption, whereas beef is known to increase it. This latter fact, plus the possibility that iron chelates, being less easily dissociated, would be better tolerated by the gastro-intestinal tract, than even the organic salts of iron, like gluconate, succinate and fumerate, led us to compare a preparation of aminoates with two of the organic salts, ferrous gluconate and ferrous succinate, and also with iron given intramuscularly.

Furthermore, there is an increasing incidence of death in children following the ingestion of therapeutic iron preparations. Reissmann *et al.* (1955) showed that "dissociable iron salts in toxic doses were rapidly absorbed through the histologically intact mucosa, both from the small and from the large bowel" and suggested (Reissmann and Coleman, 1955) that "in iron poisoning the catabolism of the organic acids is interfered with, possibly by an effect of iron ions upon enzymes in the Krebs cycle".

Franklin *et al.* (1958) showed that "the chelation of iron minimized its toxicity and provided a high factor of safety against fatal poisoning".

The amount of iron given was the same for each preparation, allowing a 35 per cent rate of absorption for oral iron. The therapeutic efficiency was assessed by measuring the mean daily haemoglobin rise in all patients. The haemoglobin percentage was estimated in the ninth and seventeenth days after the beginning of treatment. This relatively short time was used because the absorption of iron when effectively utilized gives a haemoglobin percentage rise which is represented on a graph by an almost straight line.

This fact permits calculation of the daily percentage haemoglobin rise by dividing the total haemoglobin rise by the number of days on treatment. The haemoglobin estimations were made by a number of skilled technicians, and, in a relatively large series of cases such as this, any error due to the human factor would cancel out in the final figures.

The photo-electric method was used for the haemoglobin estimations, and the technicians were not told that they had taken part in the investigations until after the final results of the trial were known. Any rise in the haemoglobin concentration due to pure chance was therefore eliminated as far as was humanly possible.

The three oral iron preparations were each administered in a dosage of two tablets three times a day, for seventeen days. A single tablet of each preparation contained 35 mg. of elemental iron. The intramuscular iron was given in a dosage of 200 mg. daily for six successive days.

In all, 994 patients (Table I) were treated. Of these 668 were followed up completely and were suitable for analysis.

They were divided into three groups:

(1) Those with a postnatal hypochromic anaemia.

TABLE I

	Postnatal			Antenatal			Medical		
	Treated	Followed Up	Daily Hb. Rise Per cent	Treated	Followed Up	Daily Hb. Rise Per cent	Treated	Followed Up	Daily Hb. Rise Per cent
Ferrous gluconate	140	75	0·9	64	50	0·7	—	—	—
Ferrous succinate	152	80	1·0	65	50	0·8	—	—	—
Iron Aminoates ..	159	85	1·0	69	50	0·8	89	79	1·2
Intramuscular iron	170	129	1·1	66	50	0·9	20	20	1·1
Total	621	369		264	200		109	99	

(2) Those with an antenatal hypochromic anaemia.

(3) Those with hypochromic anaemia from diverse causes, other than pregnancy and free from complications which would interfere with haemopoiesis.

Groups 1 and 2 were used for the comparison of all four methods of treatment.

The medical series, Group "B", being much smaller, was devoted largely to a clinical trial of the iron chelates in order that this haematinic could be used in as wide a variety of cases as possible, and was compared with a series of cases treated with imferon. The same fixed dosage was used as in Groups 1 and 2.

Antenatal and Postnatal Anaemia

The haemoglobin estimations of lying-in patients were made on the third day of the puerperium, as the total blood volume, red cell volume, haemoglobin and haematocrit value have by then returned to normal (Tysoe and Lowenstein, 1950). Anaemia detected at this early stage allows time for treatment during the lying-in period which is important in the establishment of breast feeding and prevention of puerperal sepsis.

Many patients make their first attendance late in pregnancy, and many fail to attend the anaemia clinic after confinement, so that the rate at which iron deficiency anaemia can be cured is very important.

We believe that all antenatal patients with a haemoglobin of 85 per cent or less should be given treatment, particularly as the fall in serum iron and the rise in iron-binding capacity of the serum that takes place in late pregnancy indicates a true iron deficiency anaemia, rather than a physiological anaemia. Nevertheless, in order to avoid criticism on this count, we have included in our trial consecutive series of antenatal and postnatal patients, in whom the haemoglobin was 70 per cent or less, and, therefore, below what could be regarded as physiological anaemia.

All cases, both pregnant and medical, were fully investigated, the routine adhered to being full peripheral blood examination, and, where indicated, examination of the sternal bone marrow, estimation of serum bilirubin and red cell fragility, a search for occult blood in the faeces on three successive occasions, performance of direct Coombs test, and barium meal examination.

Patients suffering from an intrinsic blood condition or megaloblastic anaemia of pregnancy were rejected from this series. All the patients were on a normal diet and no other haematinics were prescribed.

Results

The relationship between the patients treated with oral iron and those treated with intramuscular iron was the same as we had found in our previous investigations (Cope *et al.*, 1956). The rate of improvement was slightly greater in the antenatal series with intramuscular than with oral iron, but the difference was not sufficient to make this the method of choice, except in cases refractory to, or unable to take oral iron, cases first seen late in the pregnancy and patients known to be unreliable.

The rate of improvement was no greater than in the previous series for either oral or intramuscular iron, despite the fact that the oral iron was doubled from 105 mg. elemental iron per day to 210 mg., and the intramuscular iron from 600 mg. in six daily doses, each of 100 mg., to 1,200 mg. in six daily doses, each of 200 mg.

The various oral iron preparations all gave satisfactory results, the chelated iron giving the same daily haemoglobin rise both in the antenatal and postnatal series, as ferrous succinate and a slightly greater rise than ferrous gluconate.

There were no untoward side effects with any of the drugs in the postnatal series. These were all hospital in-patients, and none of them were refractory to oral iron.

The antenatal patients were treated as out-patients, whereas in our previous series the patients treated with intramuscular iron were in-patients. In this antenatal group, two patients treated with ferrous gluconate failed to respond and were treated successfully with imferon. One patient vomited following ingestion of the tablets and treatment was discontinued. This patient also responded to imferon.

Two of the patients treated with ferrous succinate were refractory to oral iron, but responded to intramuscular iron. There were no untoward side effects in this series.

Two of the patients treated with iron aminoates failed to respond, and were treated successfully with intramuscular iron. Treatment with iron aminoates caused diarrhoea and vomiting in one patient. This patient had the same reaction when given intramuscular iron and was finally treated with blood transfusion.

Five patients treated with intramuscular iron had side effects of such severity that treatment had to be discontinued. This was presumably due to a toxic level of serum iron. It is of interest that none of the patients in our previous investigation who were given only 100 mg. daily and treated as in-patients had severe reactions.

One of the patients, as previously mentioned, had diarrhoea and vomiting and was treated with blood transfusion, and one other patient who was near term and had a general reaction was treated with blood transfusion, and the other three, who also had general reactions, were treated successfully with ferrous succinate.

In the medical series 20 patients were treated with intramuscular iron, all of whom responded satisfactorily and none had untoward side effects. Eight of these had post-gastrectomy iron deficiency anaemias, refractory to oral iron. Seven had nutritional iron deficiency anaemias, refractory to iron; 2 had iron deficiency anaemia following haemorrhage from peptic ulcer; 2 had severe iron deficiency anaemia not previously treated, and 1 had iron deficiency anaemia in association with rheumatoid arthritis which had been controlled with prednisolone.

Eighty-nine medical patients (Table II) were treated with iron aminoates, of whom 79 were included in the series, as they had been adequately followed up. Of these 18 had anaemia following gastro-intestinal haemorrhage which was considered to have stopped. These all had very severe anaemia, and responded extremely well.

In 13 cases the cause was considered to be dietetic in association with excessive menstruation. This is one of the commonest associations seen in the medical haematological clinic, and in most of these cases the excessive menstruation continued during treatment. The daily haemoglobin rise was, nevertheless, satisfactory.

TABLE II

Medical Series Treated with Iron Aminoates

Cause of Iron Deficiency Anaemia	No. of Cases	Average Daily Hb. Rise Per cent
Gastro-intestinal haemorrhage ..	18	1·4
Dietetic and associated menorrhagia	13	1·1
Nutritional	9	1·4
Rheumatoid arthritis	9	1·0
Following pneumonia	6	1·1
Idiopathic	6	1·1
Hypochromic anaemia associated with controlled pernicious anaemia ..	4	1·1
Myxoedema	4	1·1
Carcinoma of stomach	3	1·2
Miscellaneous	7	1·1

The cause was purely nutritional in 7 cases, and in these the results were very satisfactory. There were 9 cases with severe long standing rheumatoid arthritis, including 2 with generalized rheumatoid arthritis of the spine. These were all responding reasonably well to prednisolone, 5 mg. t.d.s., and all the associated anaemias responded to iron aminoates.

Six cases developed moderately severe anaemia, following pneumonia. The pneumonia was controlled with antibiotics before the iron aminoates were given. In 6 cases there was an intense iron deficiency anaemia for which no cause could be found, despite thorough investigation, and the exclusion of such conditions as idiopathic steatorrhoea and malignancy. This appears to be a fairly common type of anaemia, which occasionally does not respond to iron by mouth and has to be treated by injection. These cases, however, all responded to oral iron.

Four cases had pernicious anaemia who developed iron deficiency anaemia whilst under the control of liver extracts. All 4 responded satisfactorily. The 4 patients with myxoedema responded despite the fact that myxoedema does not respond to thyroid in the first three weeks. The anaemia in the 3 patients with carcinoma of stomach was treated successfully before operation.

The miscellaneous group included cases of ulcerative colitis, nephritis, post-malarial anaemia, phthisis and various septic conditions, all of which responded.

In this series of cases of hypochromic anaemia, due to a variety of medical causes, all the patients responded satisfactorily to chelated iron at a rate comparable with those treated with intramuscular iron, and with the series of cases that we have previously published that have been treated with other oral iron preparations. There were no untoward side effects and the drug was well tolerated.

Summary

A therapeutic comparison is made of the values of a chelated iron preparation, iron aminoates, with similar amounts of iron given orally as ferrous succinate and as ferrous gluconate, and with iron given intramuscularly in the form of a dextran-iron complex, in cases of hypochromic anaemia in pregnancy and the puerperium.

A similar amount of iron in the form of iron aminoates was also given to a series of medical patients free from complications which would interfere with haemopoiesis, and compared with a series of patients treated with intramuscular iron.

All three groups were treated with a dosage of iron, both orally and intramuscularly, which was double the amounts used in a previous comparative series. Doubling the dose did not increase the rate of improvement, but increased the number of undesirable side effects in the antenatal series treated with intramuscular iron.

A satisfactory response was obtained with all four preparations and there was no material difference in the rates of improvement as assessed by the daily haemoglobin rise, though in the antenatal series the improvement, as in the previous trial, was slightly quicker with imferon than with the oral iron preparations.

All the cases but one which was refractory to oral iron responded to intramuscular iron.

Acknowledgments

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A FOLLOW-UP OF THREE CASES OF ARRHENOBLASTOMA

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ARRHENOBLASTOMAS are rare tumours of the ovary, which may cause endocrine changes. The first case was reported by Pick (1905).

Meyer (1931) thought that these tumours arose originally from male directed cells, which persist in the medullary portion of the ovary. A teratomatous origin has also been suggested, but this is not widely accepted (Speed, 1953).

The arrhenoblastoma is a solid tumour of small to moderate size, but some may be very large. The cut surface is greyish, often with yellowish or haemorrhagic areas. The typical tumour shows a microscopic resemblance to testicular tissue and is called the tubular adenoma of Pick. Other tumours show varying degrees of undifferentiation and are referred to as intermediate and sarcomatoid groups (Iverson, 1947).

Hughesdon and Fraser (1953) divide these tumours into 3 groups:

(1) "Typical" or tubular adenoma group. Adenoid or solid adenoid tumours, with de-differentiation to cords, absent or minimal.

(2) "Intermediate" group. Adenoid and corded tumours, with de-differentiation to diffuse or mesenchymal growth absent or minimal (i.e., less than mature, but still largely epithelial tumours).

(3) "Atypical" group. The remainder, which form the bulk of cases.

In a long article on the histology of their case and those in the literature, they describe 13 cases of group 1 tubular adenomas consisting of tubules in lobular groups, and all these were benign, and 25 cases in group 2 with lobular arrangement of acini, solid acini, cords and epithelial clumps, 4 of which were malignant.

The largest group 3 of 76 cases showed 6 main features:

(*a*) Diffuse mesenchymal or quasi-sarcomatous pattern.
(*b*) Cell aggregates usually corded.
(*c*) Tubular formation.
(*d*) Groups of luteinized or Leydig cells.
(*e*) Clefts or cysts lined by bare connective tissue, endothelioid non-specific epithelial or goblet cells.
(*f*) An overall impression of pleomorphism.

Any of these features in the atypical group may be absent, except the first.

These tumours occur predominantly in child-bearing years (Iverson, 1947). Flannery (1950) says most cases are found between 16–60 years, but reported a case in a girl of 13½ years.

In 1953 the total world reports comprised 126 cases of arrhenoblastoma (Blewett, 1953). However, the literature is confused with reports of various pathological diagnoses of virilizing ovarian tumours, for example gynandroblastoma (Mechler and Black, 1943; Hobbs, 1949), dysgerminoma (Sobhi and Toppozada, 1948), theca cell tumour (Collins, Varino and Weed,

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1939; Banner and Dockerty, 1945; Knight, 1948; Sternberg and Gaskill, 1950), ovarian hilus cell tumour (Sternberg, 1949), masculinovoblastoma (Winsauer and Manning, 1949; Palmer and Waldrop, 1957), Leydig cell tumour (Waugh, Venning and McEachern, 1949), arrhenoblastoma (Smiley, Beer and Tandatnick, 1953; Hughesdon and Fraser, 1953).

In general, masculinization is more universal in the less differentiated types of arrhenoblastoma (Iverson, 1947) and slight or absent in the more highly differentiated tumours which show definite tubules (Speed, 1953).

Speed stated that sex hormone estimations are usually of little value and Smiley *et al.* (1953) reported that few of the cases of arrhenoblastoma have raised 17-ketosteroids. The values were usually normal even though hirsutes and an enlarged clitoris were found. They suggested that androgenic substances not excreted as 17-ketosteroids were produced by these tumours. Similar findings of true virilism without elevation of 17-ketosteroids were reported by Segaloff *et al.* (1955) in a woman of 39 years with a hilus cell tumour. In many cases in the literature, however, there was no record of the 17-ketosteroids before operation.

Cases have been reported of arrhenoblastoma occurring during pregnancy (Felicissimo Paula Xavier and de Abreu Junqueira, 1938; Brentnall, 1945a, 1945b; Falk and Mason, 1951) and in Brentnall's case the child was a female pseudohermaphrodite. Pregnancy certainly may occur after the removal of the tumour with birth of a normal baby (Novak, 1938; Lisser, Palmer and Morton, 1942; Dockerty, 1945; Goldstine, 1946).

After surgery, signs of defeminization regress quickly, but those of masculinization are slower and their disappearance is often incomplete (Iverson, 1947).

Prognosis

The tumours are clinically benign in 80 per cent of cases (Speed, 1953), but recurrences have been reported (Novak, 1944) and out of 78 cases Henderson (1951) found reports of 12 recurrences with death (15 per cent). Varangot (1952), in a summary of the knowledge of all masculinizing tumours of the ovary, stated that 25 per cent of these patients died from metastases within 5 years.

Clinical Picture

The clinical picture resulting from the development of an arrhenoblastoma is variable, depending on whether the tumour produces endocrine symptoms or not. In the absence of endocrine effects, the signs may be only those of a pelvic tumour of size varying from that of an egg, to a full-term pregnancy. If the tumour produces androgenic substances, the first signs are those of defeminization, blending into masculinization. Clinical examination may reveal a palpable tumour in the pelvis—often quite large—but sometimes undetectable. The course of these changes is usually quite slow and progressive over several months.

Diagnosis

Although some degree of hirsutes is a very common finding in women and often causes much embarrassment and distress, it is rarely found to be due to a pathological source of androgen production, and the history will often bring to light a racial or familial incidence which Ferriman, Thomas and Purdie (1957) term constitutional virilism. Clinical examination usually fails to reveal any other evidence of virilization such as one would expect if there were a source of abnormal androgen production. Thus there is no acne, the voice is feminine, the breasts are shapely, the clitoris is not enlarged, and the menstrual cycle is often unaltered. There is rarely any sign of the anabolic effect of androgens which increase the size and bulk of the muscles. Thomas and Ferriman (1957) investigated the incidence of hirsutes in a series of 600 female hospital patients from 15–84 years and found that, in cases with major hirsutes, the average bi-acromial width was significantly greater than for a group of subjects with a zero or low hirsutes-grading; the 17-ketosteroids excretion in the former was greater, there was a bigger incidence of oligomenorrhoea, and also a genetic background.

Experience in the treatment of women with testosterone for menorrhagia (Foss, 1938) and more intensively for advanced breast carcinoma (Foss, 1956), clearly demonstrates the pro-

gressive changes which follow. These can be divided into two stages, although there is considerable overlap. Firstly, there are the changes of defeminization with oligomenorrhoea or amenorrhoea, and possibly some gradual diminution in the size of the breasts. Secondly, there is the more obvious evidence of virilization. The skin becomes greasy owing to increased action of the sebaceous glands and acne may then follow. The voice gradually becomes deeper like that of an adolescent boy. Hair begins to grow on the upper lip, chin and neck, around the areola, on the shoulders, back and chest, also to extend up the abdomen to the umbilicus, and to increase on the thighs and legs. Often there is loss of frontal hair, sometimes progressing to male-type baldness. The clitoris develops, and in the course of time may measure 1 cm. in diameter across the glans which protrudes from the prepuce as it also increases in length. The greater vascularity of the glans is shown by a bright pink colour, and the patient is continually conscious of irritation of this organ, which in some subjects leads to heightened libido (Foss, 1951) and there is increased secretion of smegma.

The anabolic effects of prolonged therapy are an increase in weight due to nitrogen and sodium retention, and a well-marked development of muscle mass, giving to the body some of the features of the male physique.

Now these changes are more noticeable in some cases than in others; there is a considerable individual susceptibility and response of the target organs to this androgen stimulation. Various factors influence the course of defeminization and virilization; naturally the type of androgen used and its rate of excretion, frequency of application, duration of action, and dosage will all modify the clinical findings from time to time. Even so, a fixed dose of 300 mg. daily of testosterone propionate will cause a varied response in different women, depending on their own endogenous hormone balance and the sensitivity of their receptor tissues.

Thus, when one sees a woman who has hirsutes, it is essential to assess the case with the greatest care, to exclude other evidence of defeminization or virilization, and even without such evidence at the initial examination a long period of observation is necessary to exclude a gradual and insidious development of the other changes. The rate of development of symptoms is important. A rapidly-growing carcinoma of the adrenal cortex will, by producing androgens, give rise to virilization within a month or two, whereas adrenal hyperplasia or an androgen-producing ovarian tumour may show a more leisurely course.

Mild or moderate cases of hirsutes often follow oral therapy with methyltestosterone, methylandrostenediol, methylandrostanolone, or combinations of these hormones with oestrogens given for dysmenorrhoea, infertility, menorrhagia, loss of weight, or menopausal symptoms, or to stimulate libido. A careful history should exclude such treatment, and 17-ketosteroids estimation will show normal values as these methylated androgens do not raise the 17-ketosteroids excretion.

Virilization can occur at any age beginning with the female pseudohermaphrodite with a congenital disorder of steroid metabolism in the adrenal cortex. Superimposed on the changes of virilization already mentioned, the effects of androgens on the external genital apparatus *in utero* in the pseudo-hermaphrodite and the changes induced in the growth of the skeleton with its consequent anthropomorphic features in all pre-pubertal cases, are of diagnostic importance. After puberty, defeminization and increasing virilization are the only changes seen, while following the menopause there is merely a progressive virilization, sometimes associated with obesity.

In the case which shows evidence of the onset of defeminization or virilization, investigation has to prove whether there is indeed abnormal or excessive androgen production, and then to determine its source, which more commonly is the adrenal cortex, and comparatively rarely, the ovary.

Clinical examination may reveal a palpable tumour in the pelvis associated with or without a raised 17-ketosteroids excretion. If the 17-ketosteroids are raised and a tumour is not detected in the pelvis a short course of prednisolone should be given to suppress the adrenal cortex by inhibiting secretion of adrenocorticotrophic hormone (A.C.T.H.); 2·5 mg.

prednisolone 4 times daily is quite adequate. A marked reduction of 17-ketosteroids excretion after a week will indicate an adrenocortical origin of androgen over-production due to cortical hyperplasia. If no change occurs and there is a history of rapid virilization, the condition is likely to be due to adrenocortical carcinoma, and a tumour may often be felt in the upper abdomen, but if the symptoms develop slowly, one should expect to find a virilizing tumour of the ovary. Laparotomy is then essential and will usually clinch the diagnosis. However, Jeffcoate (1958) claims that culdoscopy is worthy of consideration. A patient on whom this procedure was carried out proved to have an arrhenoblastoma which was not palpable during examination under anaesthesia, and which produced atypical symptoms. If there is no definite evidence of a unilateral ovarian tumour, it is probably wise to incise both ovaries and to take a wedge-shaped biopsy, passing through the hilum which may show hyperplasia or tumour of these vestigial Leydig-like hilar cells. Actual tumours of the ovary producing virilization may be due to adrenocortical rests, Leydig cells and luteal tissue.

During the last 12 years, 3 cases of arrhenoblastoma have been under observation for 12½, 12¼ and 5 years respectively.

Case Records

Case 1

A married woman (E.E.) was seen on 16th January, 1946 at the age of 22 years. She had her menarche at 14 years with a menstrual history of 3–4/28 and scanty loss. Her appendix was removed when she was 19 years and she married shortly after in June, 1943. Menses occurred in June and August, 1943, followed by amenorrhoea until January, 1944, which was her last period. She was discharged from the Services as it was thought that she was pregnant. She noticed gradual deepening of the voice and growth of facial hair after January, 1944.

On examination she had a normal slim figure. Her voice was deep like that of a boy at puberty. There was moderate growth of hair around the breasts, which were of average size, and on the chin, and pubic hair grew up the abdomen in male configuration. Her clitoris was enlarged; 2·5 cm. long, and 1 cm. in diameter. There was a small mass palpable in the pouch of Douglas. At laparotomy the right ovary was apparently normal, and what appeared to be a follicle cyst of the left ovary was found. This large cyst was easily shelled out from the normal ovarian tissue, and the ovarian incision closed. There was a rather stormy convalescence, and 23 days after removal of the tumour the patient menstruated.

The mass, 7·5 cm. in diameter, consisted of several small cysts and a more solid portion of yellowish glairy consistency. Microscopically the structure was diverse, consisting partly of clear, pale cells, diffusely scattered through a fibrous matrix, and partly of columns and strands of deeply staining cells of doubtful origin, but having some resemblance to testicular adenoma. A diagnosis of arrhenoblastoma was justifiable (Fig. 1).

Before discharge from hospital, her larynx was examined by Mr. Scarff who stated that "the vocal cords were much broader than normal for a woman's larynx, but not longer".

She continued to menstruate at intervals of 4–5 weeks until she became pregnant at the end of 1947 and bore a normal child. In October, 1949 excretion of 17-ketosteroids was 19·7 mg./24 hours.

She has been followed up since then and gave birth to a normal child in 1954. In August, 1958 her general health was good and there has been no sign of recurrence. Her menses were irregular with intervals of 4–6–8 weeks, lasting 6–8 days. There was still some facial hirsutes, but the body distribution of hair was normal and her weight was steady at 9 stone.

Case 2

This patient (E.B.) was first seen on 16th April, 1946 when aged 16½ years for hirsutes and primary amenorrhoea. She had been a normal child until 14 years when she developed acne on her face and back, and hirsutes for which she used pumice abrasion or plucking for her cheeks, upper lip, and legs. Her voice also became deep and she was addressed as "Sir" on the telephone. Her breasts had not developed very well, and she complained of lumps in both.

On examination her height was 66½ inches (169 cm.), span 71 inches (180 cm.), and weight 10 stone (63·6 kg.). She had a reasonably normal figure with small nodular breasts, but rather large hands and strong muscles. There was a thick growth of black stubble on her cheeks, upper lip, and chin, which had not been removed when first seen in a surgical ward after excision of a lump in one breast (Fig. 2). There was a male-type pubic escutcheon, and her chest, back, arms and legs were hairy and there was a moderate growth of long black hair around both areolae. Her skin was greasy, and there was acne on the face and back. Her clitoris was enlarged. She was examined under an anaesthetic and the uterus was hypoplastic, and no tumours were felt in the pelvis —the ovaries were not palpably enlarged. 17-ketosteroids were raised, 34·1 mg./24 hours, and an intravenous pyelogram showed that the right renal pelvis was larger than the left, lower and rather a long way from the midline. X-ray of the epiphyses showed closure.

As it was thought that she might have an adrenal tumour, a general surgeon (J.A.P.) explored her abdomen. The adrenals were apparently normal in size, but both ovaries were enlarged. On wide section of the right ovary numerous small cysts were seen, and in the centre of this ovary was a pinkish brown area of tumour.

The appearance of the left ovary was similar with small cysts and occasional haemorrhagic areas. Unfortunately it was thought wise at the time to remove both ovaries. Convalescence was uneventful.

Pathology. The right ovary measured 5·3×3·6×2·8 cm. and weighed 29 g. The left ovary measured 4·8×2·2×3·3 cm. and weighed 20 g. The surface of each was smooth, white and opaque resembling the tunica albuginea of the testes. On section, the right ovary contained small cysts ranging from 1–6 mm. in diameter and containing clear fluid and a few contained altered blood. In the centre of the ovary was a pinkish brown area measuring 2·5×1·5 cm. and this tissue was softer and more vascular than the general fibrous stroma of the ovary.

The left ovary was similar and polycystic, but there was no pink tissue as in the right ovary.

Histology. The tunica measured 300 microns in thickness. The cortex contained numerous primordial follicles in various stages of development. There were numerous follicular cysts lined by granulosa cells. The pinkish tissue in the medulla of the right ovary consisted of a group of different kinds of cell. Some were large, about 15 microns in diameter, with pale vacuolated cytoplasm arranged in clusters with nuclei of 5–8 microns. In places these cells resembled the interstitial cells of the testis. Frozen sections stained with Sharlach R. revealed lipid in their cytoplasmic vacuoles. Only a little lipid was doubly refractile. Between these groups of large and relatively pale cells were some smaller ones which were darker, measuring 5–8 microns with scanty cytoplasm and dark nuclei, some of which showed mitoses; these were arranged in cord-like groups.

There were also some cells intermediate in character between the small dark ones and the large vacuolated ones.

The tumour of the right ovary was an arrhenoblastoma (Fig. 3) and there was only a very imperfect attempt at tubule formation, but numerous interstitial cells containing lipid were present.

In July, 1946 this patient's 17-ketosteroids were 12·5 mg./24 hours and she was implanted with 400 mg. stilboestrol. Her acne had disappeared (Fig. 4).

By September, 1948 she plucked her face only at weekends. 17-ketosteroids excretion was 10·5 mg. She was then taking dienoestrol, 5 mg. twice daily for 14 days each month, and had regular menses.

In October, 1949 17-ketosteroids excretion was 12·2 mg./24 hours, and an implantation of 200 mg. oestradiol was carried out, followed by cyclical ethisterone therapy, 25 mg. 3 times daily for 7 days, each month. In May, 1950 she married and went to live in Ireland, and was next seen in March, 1953; coitus was dry and she was suffering from oestrogen deficiency as she had been unable to afford hormone therapy in Dublin. A further implant of oestradiol 200 mg. was carried out with cyclical ethisterone, followed by regular menses and considerable improvement in general health. There had been no reduction in the size of the clitoris, but this was no longer turgid.

In 1954 she took up residence in London and was transferred to the care of Dr. A. W. Spence, and she continued treatment for 2 years.

In June, 1957 she had omitted cyclical ethisterone therapy for the preceding year owing to her occupation and changed residence. Bleeding had occurred regularly although more scantily until she discontinued taking ethisterone. She had no flushes or sweats, but complained of feeling worn out and tired. Although libido was good and coitus occurred with adequate lubrication 4 times weekly, her difficulty was to achieve orgasm. Her clitoris had been extremely sensitive for the last 12–18 months, and she could not bear to have it stimulated by her husband; previously such sexual stimulation had been pleasurable.

She had increased in weight from 9 stone 13 pounds (63 kg.) in 1950 to 11 stone 5 pounds (72 kg.) but at a distance looked an attractive woman of 27 years. Her breasts were small and her figure normally feminine. On the upper lip there was short black downy hair, while on the cheeks the hairs were coarser, and there was short black stubbly hair around the chin. There was no hair on the upper arms or trunk except for a ring of coarse black strands around the areolae, and pubic hair extended to the umbilicus, but was not profuse.

The vulva was smooth but not atrophic, the clitoris measured 1 cm. across, and the pale glans protruded from the prepuce. The uterus and cervix were normal.

Since then she had been taking cyclical therapy with stilboestrol, 5 mg. 3 times daily and ethisterone 25 mg. 3 times daily, together for 10 days each month. In addition to regular withdrawal bleeding, libido had greatly improved, and coitus was completely satisfactory.

Case 3

An unmarried girl of 27 years (E.F.) was first seen on 3rd June, 1953. She had noticed gradual increase in growth of facial hair over the previous year, particularly in the preceding 9 months. There was also increased hair on the lower legs and thighs. Her menses had started at 15 years and were regular 5/35 until October, 1952, when there was staining only for 2 weeks. Another scanty period lasted 3 days in November, after which she had a slight show every 14 days for 3 months. Her doctor gave her tablets of oestrogen and ethisterone which increased the flow. No voice change had been noted; her weight remained steady.

On examination she had a slim figure and normal voice. The height was 66 inches (168 cm.), the span 66½ inches (169 cm.), and the weight 8 stones 4 pounds (53 kg.). There was quite a profuse growth of long black hair extending down the sides of the cheeks, around the chin, upper lip, and upper part of the neck (Fig. 5). Pubic hair stretched in a thick black line up to the umbilicus, and downwards over the upper thighs. There was slight acne on the face and back. Her breasts were small in keeping with her slim figure. The clitoris was enlarged to 0·6 cm. in diameter, and longer than normal, and the glans protruded from the prepuce (Fig. 6). Pelvic examination revealed a firm swelling in the left fornix which was thought to be ovarian. The 17-ketosteroids excretion was 31·4 mg./24 hours.

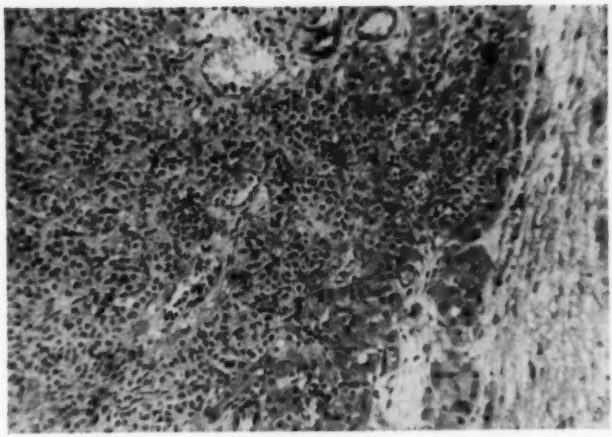

FIG. 1

Case 1. Arrhenoblastoma. H. & E. ×125.

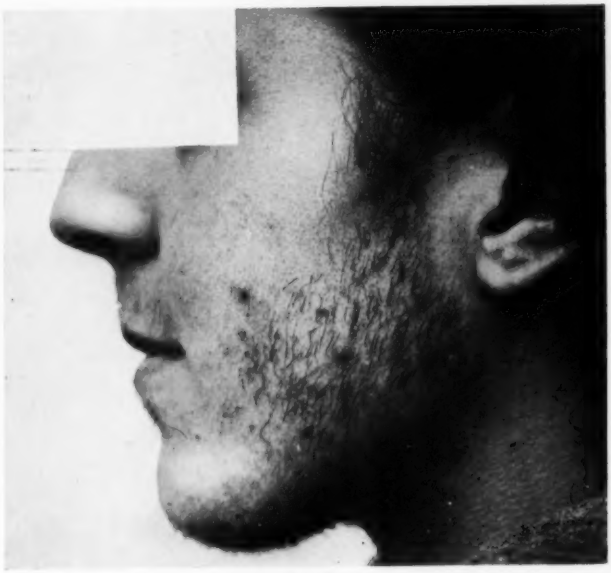

FIG. 2

Case 2. 15th April, 1946. Face not plucked for 10 days.

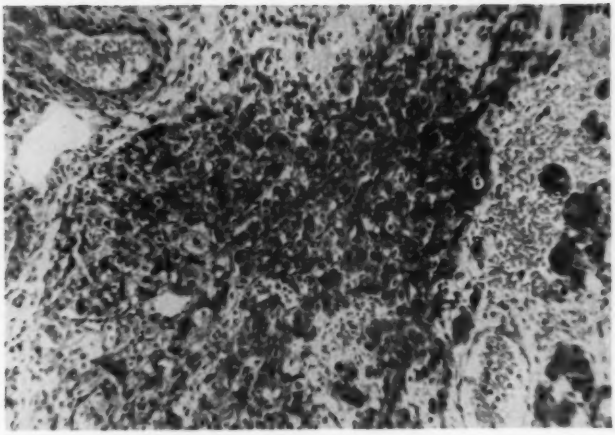

FIG. 3
Case 2. Arrhenoblastoma. H. & E. ×150.

FIG. 4
Case 2. Photograph 8 weeks after oöphorectomy. Face not plucked for 10 days.

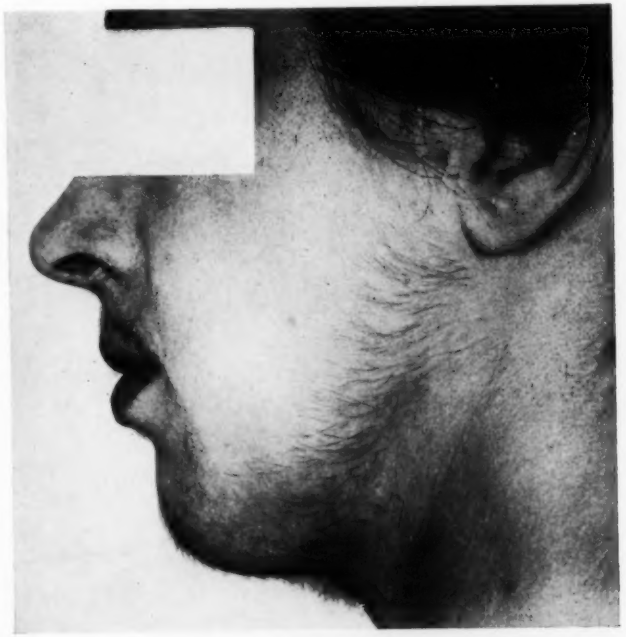

FIG. 5
Case 3. 10th June, 1953.

FIG. 6
Case 3. Enlarged clitoris.

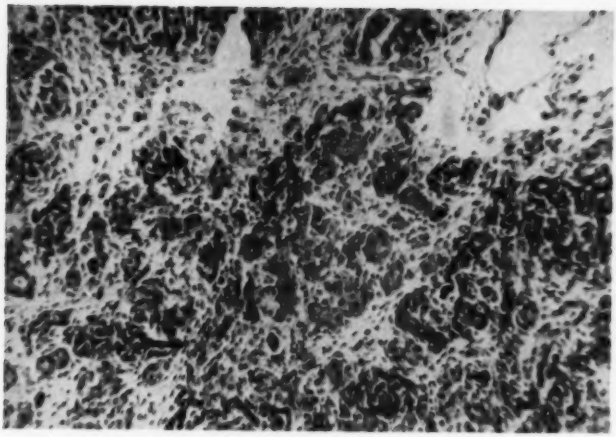

FIG. 7
Case 3. Arrhenoblastoma. H. & E. ×150.

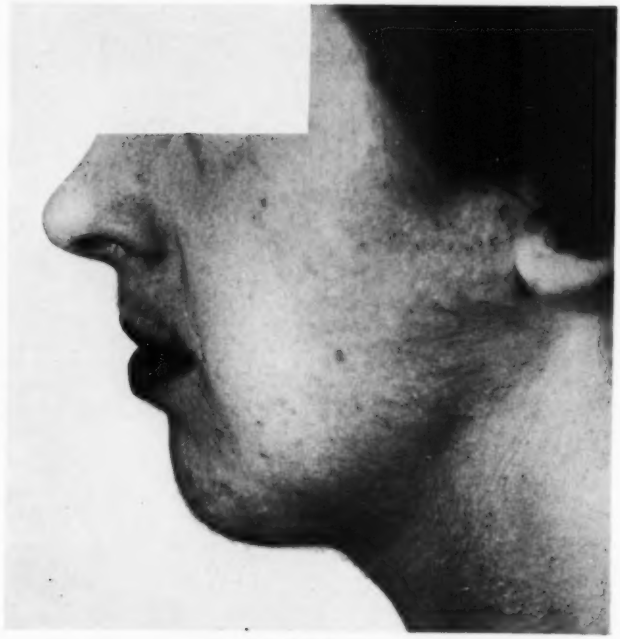

FIG. 8
Case 3. Photograph 10 months after oöphorectomy.

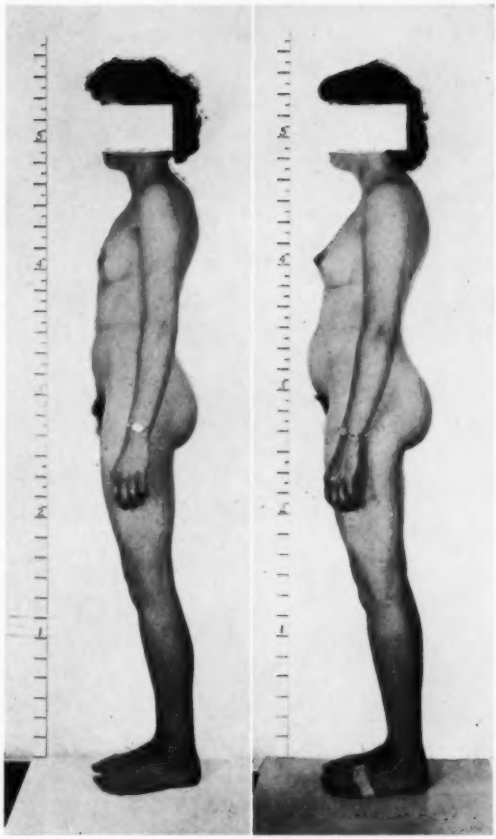

FIG. 9

Case 3. Photographs taken before and 10 months after operation showing increased breast development.

At laparotomy on 2nd July, 1953 she was found to have a tumour of the left ovary the size of an orange. The right ovary, which was apparently normal, was incised and explored. Left oöphorectomy was performed.

The tumour, which was oval, soft and well encapsulated, measured 6·5×5 cm. on section showing a cut surface which bulged with lobulated yellowish-brown tumour tissue; the lobules were separated by glairy pale glistening trabeculae of oedematous connective tissue. Microscopically, the structure was typical of arrhenoblastoma (Fig. 7). In some of these areas there were cord-like groups of cells with dark-staining nuclei, and in other areas there was an appearance of tubular formation with a peripheral arrangement of elongated nuclei. In addition to these were larger cells with pink staining cytoplasm, similar to the Leydig cells of the testes, scattered between the cords. In places the strand-like areas of dark blue staining nuclei were interspersed in a loose network of connective tissue.

Six days after operation, the 17-ketosteroids excretion had fallen to 4·7 mg./24 hours and the figure was 10·7 mg./24 hours 6 months later and 8·8 mg./24 hours 1 year after operation.

Menses returned 50 days following oöphorectomy and recurred regularly at 26–28 day intervals with normal loss.

In May, 1954 she was very well, the facial hair was less (Fig. 8), her bust measurement had increased from 31 inches to 35 inches (78–88 cm.), and she was 14 pounds (6·35 kg.) heavier (Fig. 9).

She married on 9th January, 1954 and, when seen on 23rd June of that year, she had had amenorrhoea since 8th April, and a pregnancy test was positive, but unfortunately she miscarried at 16 weeks.

In 1955 this case was presented briefly to the North of England Obstetrical and Gynaecological Society (Leverton, 1955).

In May, 1957 her general health was good, the weight was 8 stone 10 pounds (55·5 kg.), the menses were regular every 26–27 days lasting 5–7 days, but no further conception had occurred and she was being investigated by a gynaecologist. She still had to remove a little hair from her chin every few days with tweezers.

In August, 1958 her periods had been regular until April when she became pregnant again, but unfortunately she aborted at about the tenth week; the foetus was not apparently deformed or macerated. There was no change in her voice, and she weighed 8 stones 7 pounds (54 kg.). The hirsutes was still troublesome, but she managed to deal with this with tweezers.

Discussion

In all 3 cases endocrine changes were noted and their onset was gradual from 1–2½ years, before their reference to the gynaecologist (H.L.S.).

In the first case, amenorrhoea was the first symptom with progressive growth of hair on the face, chin and abdomen. Case 2 did not have the menarche at the average age (13) and then began to develop hirsutes at 14 and amenorrhoea persisted until she was seen at 16½ years. Case 3, however, noticed gradual increase in facial hair over a year before diagnosis, whereas

Table I

Main Features of Three Cases of Arrhenoblastoma

Case	1	2	3
Age of onset	20 years	14 years	26 years
Date seen	26th January, 1946	16th April, 1946	3rd June, 1953
Age first seen	22 years	16½ years	27 years
M. or S.	M.	S.	S.
Menses	Amenorrhoea 2 years	Primary amenorrhoea	Oligo and hypomenorrhoea
Hirsutes	++	++++	+++
Voice	Deep	Deep	Normal
Clitoris	+	++	++
Breasts	Normal	Small	Small
Tumour	Palpable	Not palpable	Palpable
17-ketosteroids before	—	34·0 mg./24 hours	31·4 mg./24 hours
Operation	Local removal	Bilateral oöphorectomy	Oöphorectomy
17-ketosteroids after	—	10–12 mg./24 hours	4–10 mg./24 hours
Return of menses	23 days	Substitution therapy	50 days
Pregnancy	2 boys	—	2 miscarriages 4/12, 10/52
Hirsutes	Slight	Moderate	Slight
Voice	Deep	Deep	Normal
Duration of follow-up	12½ years	12¼ years	5 years

her menses had persisted until 4 months before.

The first 2 patients had deepening of the voice, and it is interesting to note that Case 3 had developed hirsutes before amenorrhoea, but had no voice-change.

All 3 had enlargement of the clitoris.

It is, therefore, wise not to be too dogmatic about the accepted sequence of events of defeminization followed by virilization. Previously it was reasonable to exclude an androgen-producing endocrine abnormality if there was no enlargement of the clitoris, but in a report by Jones and Everett (1946) the history of a woman aged 36 is described with oligomenorrhoea, considerable hypertrichosis, and a normal clitoris with slight enlargement of one ovary which at laparotomy proved to contain an arrhenoblastoma.

In 2 of our cases the 17-ketosteroids were moderately elevated before operation (the other 17-ketosteroids estimation was not carried out). However, it is evident from the literature that this is not invariably so. Smiley *et al.* (1953) suggested that there may be androgenic hormones which are not excreted as 17-ketosteroids.

In established and reported cases of arrhenoblastoma, there is usually always hirsutes, which may precede menstrual irregularity or change in amount or cessation, but Iverson (1947) describes a woman who developed a pelvic tumour at the age of 61 years. She had been hirsute since 25 years but her menopause did not occur until 55 years, and voice changes were not evident until 59 years.

Therefore, cases of hirsutes should always be followed up for many years in the absence of other diagnostic features, and the possibility of an arrhenoblastoma should always be considered after other pathological entities have been excluded. In general, virilism due to adrenal cortical hyperplasia is of moderately rapid development, and that due to cortical carcinoma has a very short history. As Jeffcoate (1958) has observed, culdoscopy might be worth while in many more cases of so-called idiopathic hirsutes, and, if there is any real doubt, laparotomy is justified.

It is quite certain that a possible ovarian source of abnormal androgens cannot be excluded without a long-term follow-up of cases.

It is said (Iverson, 1947; Falk and Mason, 1951) that endocrine changes are more universal in the less differentiated types of arrhenoblastoma, and these 3 cases, probably falling into the intermediate group, agree with that theory. However, Iverson (1947) says it is impossible to grade the 3 types of arrhenoblastoma accurately, and that there is no real correlation between primitivity and degree of masculinization. Hughesdon and Fraser (1953) describe 13 cases of tubular adenoma with considerable differentiation as benign, whereas in the same series, 4 out of 25 in the intermediate group were malignant, and the overall rate of malignancy in these tumours has been stated by Varangot (1952) to be 25–27 per cent. Presumably there is more likelihood of malignancy in the de-differentiated or largest group of cases which show endocrine changes and histologically diffuse mesenchymal or a quasisarcomatous pattern (Hughesdon and Fraser, 1953).

Long follow-up studies are not often described, but in this small group, the patients are fit and well without any sign of recurrence after 12½, 12¼, and 5 years respectively.

Summary

The literature, clinical picture, diagnosis, prognosis, and pathology of arrhenoblastoma are reviewed. Three fresh cases showing endocrine changes, and classified in the intermediate group histologically, are described. No metastatic change has been found during periods of observation of 12½, 12¼, and 5 years.

Acknowledgments

Our thanks are due to Mr. H. L. Shepherd for allowing us to report these cases, to Professor T. F. Hewer and Dr. A. L. Taylor for the pathological reports, and to Mr. Godman of the University Medical Photographic Department for the clinical photographs, and to the University Department of Pathology for the photomicrographs. Mr. J. A. Pocock operated on Case 2.

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PLACENTA PRAEVIA

A Review of 242 Cases and the Principles of Management

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MACAFEE (1945, 1949) has been very prominent in drawing attention to the conservative management of cases of placenta praevia. He has stated concisely the guiding principles in these words ". . . placenta praevia is not an obstetrical emergency which must be dealt with at the first haemorrhage", which is of course a complete negation of Jaggard's formerly time-honoured dictum that "there is no place for the expectant treatment of placenta praevia". In 1955 Grant presented 200 cases, treated on Macafee's principles, which show the best results, from the point of view of perinatal and maternal mortality, of any series yet published. He wondered from a consideration of other series whether or not Jaggard's view still held sway in some quarters.

The National Women's Hospital, from which the present series of cases originates, was established in 1947 and, from the outset, the policy in cases of placenta praevia has been on the lines laid down by Macafee in 1945. Thus an opportunity arises for independent evaluation of these principles. Since the desideratum of a zero maternal mortality has been achieved by many centres another reason for presenting a series of cases is to examine closely the means whereby perinatal mortality may possibly be reduced still further.

GROUPING OF CASES

The 242 cases to be considered were treated in the 9 years April, 1948 to March, 1957. In these 9 years 303 cases were listed in the records but after scrutiny of all case notes 61 cases were deleted as not being proven, i.e., the placental site was not felt on vaginal examination under anaesthesia, or seen at Caesarean section, or felt before manual removal of an attached placenta. The single exception made is one case where the placenta was born vaginally before the infant (which, although premature, survived).

NUMBERS, INCIDENCE AND CLASSIFICATION

TABLE I
(Percentages in brackets)

Total	Booked Cases	Emergency Cases	Primi-gravidae	Multi-parae
242	60 (25)	182 (75)	40 (16·5)	202 (83·5)

In the period considered there were 22,620 deliveries in the hospital giving an incidence of placenta praevia of just over 1 per cent. Berkeley (1936) and Mahfouz (1939) also give a 1 per cent incidence, although later series (Johnson, 1950, 1 in 250; Westgren, 1954, 1 in 380) give lower rates. Since the diagnostic criteria are fairly strict it is likely that our true incidence is higher than 1 per cent. The explanation is seen in the high proportion (75 per cent) of emergency cases in the series. The hospital is the only public one where abnormal obstetrical cases are handled in an area with a population of approximately half

a million. The incidence amongst booked cases is 0·32 per cent, slightly over one-third of all deliveries in the hospital being emergency cases.

TABLE II

Type ..	1	2	3	4
Numbers	40	72	101	29
Per cent	16·5	29·8	41·7	12·0

The incidence shown of the more severe degrees is probably higher than actually exists since it is likely that many of the lesser degrees delivered themselves with minimal haemorrhage, and so passed unnoticed.

SEVERITY OF HAEMORRHAGE

In Table III this is shown according to type and simplified into that requiring transfusion or not. Since haemorrhage is an ever-present risk in this condition either before, during or after delivery, it does not include only those cases where the initial or any one episode of bleeding warranted transfusion but also those cases where repeated small haemorrhages produced undue lowering of the haemoglobin, where excessive bleeding during Caesarean section occurred, and where primary post-partum haemorrhage ensued.

TABLE III

Type	Numbers	Transfused	Per cent Transfused
1	40	14	35·0
2	72	31	42·1
3	101	52	51·5
4	29	22	75·5
Total	242	119	49·1

It is worthy of note that over one-third of the Type I cases, a type usually regarded with equanimity, required transfusion. This is a point which will be referred to later with regard to foetal salvage.

MANAGEMENT

In general the aim in management was to prolong the pregnancy to at least 37 or 38 weeks and so gain a more mature infant, provided this did not conflict with the safety of the mother. Co-operation from a large number of general practitioners (there is practically no domiciliary midwifery performed by either doctors or midwives in the area) has been very good in that only 2 cases were admitted having had a diagnostic vaginal examination. In 72 patients (29·8 per cent) at least a fortnight elapsed from the initial admission with a presumptive diagnosis of placenta praevia to the time of delivery. A further 30 (12·4 per cent) were in hospital from 6 to 13 days before delivery so that altogether 42·2 per cent of the patients were treated conservatively to gain a more mature infant. For such patients cross-matched blood was always ready; unless transfusion was indicated immediately two pints of cross-matched blood were made available by the laboratory and, if not used, automatically renewed every fourth day until no longer required. This constant availability of cross-matched blood was of considerable value to many of the more severe cases who had significant haemorrhages whilst being managed conservatively. One such case had a very severe haemorrhage in the X-ray department, three weeks after admission. Adequate replacement with fully matched blood was possible within minutes.

Cases at or within two or three weeks of term were not managed any more conservatively than was necessary to type and cross type blood or treat any other condition present. X-ray placentography was performed (from 1952 onwards) in all cases where indicated, i.e., in most of the early cases and in the later cases (37 weeks and onwards) where there was any clinical doubt as to the diagnosis. Wherever possible, and if placentography had not been performed, a "straight" abdominal X-ray was taken to exclude foetal abnormality. Since only 2 such cases were recorded and also because other series (Grant, 1955, mentions 2 such infants) show a similarly low incidence, and because many abnormalities are not diagnosable by X-ray, it is considered that such examination

is indicated only when possible but that it should not be made obligatory before performing Caesarean section. Severe haemorrhage and the necessity of controlling it rapidly may justify Caesarean section even though the baby be dead or deformed.

In the conservative management of suspected placenta praevia there often arises the question of what to do with the patient who has ceased bleeding, since admission, and doubts have arisen as to the correctness of the diagnosis. Often the lie of the foetus is quite stable, the foetal head has begun to settle into the pelvic brim and the radiological findings are doubtful or even negative for placenta praevia. In such cases the policy has been to allow the patient to go home if she lives within reasonable distance of the hospital and can return quickly if further haemorrhage occurs. If the head has engaged and the X-ray is unequivocally negative for placenta praevia the patient is allowed home even if she lives at a distance. No hard and fast rules can be laid down but it is felt that if due regard is given to the clinical and radiological findings it is possible to pick the patient whom it is safe to discharge. We therefore agree with Watson *et al.* (1957) that the results of radiological technique are sufficiently reliable and can be trusted—especially when negative findings are taken in conjunction with clinical evidence. Many obstetricians will quarrel with this view and possibly some (Olney, 1957) will make gloomy prophecies of disaster. We can only say that since we have learned how helpful and reliable radiology can be in the diagnosis of placenta praevia we have discharged undelivered many patients over the last 5 years with a history of vaginal bleeding late in pregnancy, and have not yet had cause to regret it.

Treatment

Treatment according to the degree of placenta praevia is shown in Table IV.

Table IV

Treatment	Type 1	Type 2	Type 3	Type 4	Total
Caesarean section	19	57	92	28	196
Artificial rupture of membranes and/or vaginal delivery ..	19	12	6	1	38
Breech extraction	1	2	2	—	5
Artificial rupture of membranes and Willetts forceps ..	1	1	1	—	3
Total cases	40	72	101	29	242

Table V

Author	No. of Cases	Percentage Incidence of Caesarean Section	Maternal Mortality (Per cent)	Perinatal Mortality (Per cent)
Fitzgerald *et al.*, 1954	283	19·4	0·7	59·2
Parks and Barter, 1950	187	31·1	Nil	52·8
Westgren, 1954	356	45·0	2·9	38·0
Stallworthy, 1951	245	40·0	0·4 (not associated)	18·0
Macafee, 1949	275	46·0	0·72	20·0
Grant, 1955	200	76·0	Nil	11·9
Present series	242	81·0	Nil	12·6

The incidence of Caesarean section is thus 196 sections in 242 cases or 81·0 per cent. Seven of the operations were of the classical type, 6 in the first 2 years and only 1 in the last 7 years of the series. No apology need be given for such a high proportion of sections for a glance at a few series (Table V) of recent years should show that as regards the chief aim of obstetrics—to produce a live baby and healthy mother—there is now no place for the "old-fashioned" methods in the vast majority of cases, and that apology is only needed if the Caesarean section is not high enough.

It will be noted from Table IV that 19 out of 40 patients with Type I placenta praevia required Caesarean section. Other reasons in 9 of these were:

Toxaemia of pregnancy	2 cases
Previous successful repair for stress incontinence	1 case
Breech presentation	2 cases
Previous Caesarean section ..	1 case
Cord presentation	1 case
Misleading positive X-ray findings ..	2 cases

In the other 10 cases the amount of bleeding (including 3 with bleeding following examination under anaesthesia), and the clinical diagnosis, were sufficient to warrant Caesarean section. One case with a Type I placenta praevia required a transfusion of 3 pints of blood following a spontaneous bleeding at the onset of labour.

Results of Treatment

Since no mothers were lost this need only be considered with regard to perinatal mortality.

Table VI

No. of infants born ..	246
Total perinatal mortality	31 or 12·6 per cent
Full-term infants lost ..	10 in 179 or 5·6 per cent
Premature infants lost	21 in 67 or 31·4 per cent

Two premature infants (one with anencephaly, the other with meningocele and exomphalos) have not been corrected for since it is generally thought that placenta praevia may predispose to such abnormalities. Twenty-one premature infants (including the 2 abnormal ones) were delivered vaginally and 9 of the 19 without congenital abnormalities (47·4 per cent) were lost; of 46 premature infants delivered abdominally only 10 (21·8 per cent) were lost. Of the full-term infants the death rate was 16·5 per cent (5 in 27) for vaginal delivery, and 3·3 per cent (5 in 152) for Caesarean section. The combined rates are 7·6 per cent (15 in 198) perinatal mortality for Caesarean section and 33·3 per cent (16 in 48) for vaginal delivery. The perinatal loss for Caesarean section generally in the hospital is 6·9 per cent, averaged over the last 9 years.

Table VII

Perinatal Mortality According to Type and Contribution of Prematurity

Type	No. of Infants	Perinatal Mortality		Perinatal Mortality Associated With		Percentage Contribution of Prematurity to Type Mortality
		No.	Per cent	Prematures	Full Term	
1	42	4	9·5	2	2	50·0
2	74	7	9·5	5	2	71·4
3	101	13	12·9	10	3	77·0
4	29	7	24·1	4	3	57·1
Total	246	31	12·6	21	10	67·7

Factors in Perinatal Mortality

Table VII shows the perinatal mortality according to type and also the contribution of prematurity to that mortality.

This table shows clearly that, despite the policy of withholding interference for as long as possible in the interests of maturity of the infant, prematurity still plays a considerable part in the perinatal mortality of placenta praevia.

A further analysis of the 31 infants lost shows that haemorrhage on the part of the mother also played a considerable part in this loss, for in no fewer than 27 of the 31 cases transfusion was necessary.

Table VIII

Severity of Bleeding in 27 Cases Where Infant was Lost

Transfusion required	500 c.cm.	500–1,500 c.cm.	1,500 c.cm.+
Number of cases ..	8	12	7

The other 4 cases where the infant died were:

(1) Two premature infants with abnormalities incompatible with life.

(2) Breech delivery of a 1 pound 13 ounces infant.

(3) Full-term infant. Examination under anaesthesia following a brisk haemorrhage late in labour revealed a Type II placenta praevia and brow presentation. Infant dead before extension to face presentation and forceps delivery achieved.

The fact that haemorrhage of major degree (in the 27 such cases it was spontaneous in 25 and only twice provoked by diagnostic vaginal examinations) played such a part in perinatal mortality might seem to indicate that there is an irreducible minimum of foetal loss. In an attempt to see if it were possible to reduce infant loss still further the notes of each patient where the infant was lost were again reviewed. This showed that it seems possible that the policy of conservatism may be carried too far in some cases.

A detailed survey of these 31 cases shows that there were 20 cases where it can be considered that it was almost impossible to have salvaged the infant. In 14 of these there was sudden and severe haemorrhage, mostly preceded by one or more warning haemorrhages. There was no delay in instituting active treatment and undertaking delivery in 5 of these, but in 5 delay of from 2 to 4 hours was necessitated by the mother's condition. In one other case there was calculated delay, despite quite severe haemorrhage, because of extreme prematurity of the infant (1 pound 13 ounces). In another case the patient herself actually delayed calling a doctor until her own condition was parlous and the infant dead. The remaining 6 of this group of 20 cases comprised infants whose mothers all had persistent haemorrhage giving rise to concern but which were all 3½ pounds and less in weight. It is possible that earlier Caesarean section might have saved one or two of this group but in the presence of such a degree of prematurity this is very doubtful. Table IX summarizes this group.

Table IX

"Unsalvageable" Group—20 Cases

Severe haemorrhage:	
No delay in treatment	5
Delay for maternal condition	5
Delay by patient	1
Delay for extreme prematurity	1
Total	12
Persistent but not alarming haemorrhage: Infants 3½ pounds and less	6
Abnormal infants	2

This leaves 11 cases where possibly with different obstetrical management the infant might have been saved. In 2 of these cases there was severe haemorrhage provoked by vaginal examination before admission. One of these had actually had two examinations, one for surgical induction for mild toxaemia (despite two previous small warning haemorrhages) which provoked some bleeding, followed by a further examination to find out the cause of the bleeding. Severe bleeding ensued and the patient was then sent 30 miles by ambulance to the hospital. It is a fortunate chance that this patient did not become the only maternal loss. The other case

examined vaginally had been admitted to a small public hospital in the city dealing mainly with normal cases and examined there. The infants in these 2 cases and in another where there was unaccountable delay by the referring doctor in sending the patient to hospital were all dead on admission of the mother. Infant loss in such cases can only be avoided or lessened by education of the general practitioners handling maternity cases. All 3 cases occurred prior to 1953 and the establishment of regular teaching courses for practitioners as part of the activities of the University of Auckland Postgraduate School of Obstetrics and Gynaecology.

In the remaining 8 cases it is possible that conservatism may have been carried too far and that earlier interference, particularly in the direction of Caesarean section, might have salvaged all 8 infants. All infants were 4 pounds or more in weight and therefore of reasonable maturity, and in every case persistent haemorrhage which had failed to settle following admission had given warning that a conservative policy was unlikely to give a more mature infant before labour ensued. A summary of these cases is given here:

Case 1. 50.2428

Persistent alarming loss after admission at 34 weeks was allowed to continue for 24 hours before examination under anaesthesia showed a Type IV placenta praevia and Caesarean section was undertaken. The 5-pounds infant died 24 hours later.

Case 2. 50.3454

The history was almost exactly the same as in Case 1 except that it was a Type III placenta praevia and the infant weighed 5 pounds 3 ounces. It is easy to be wise after the event of course but conservatism would seem to have been allowed to degenerate into procrastination in these 2 cases.

Case 3. 51N.253

Persistent loss for 24 hours following admission at 35 weeks. One severe loss gave rise to foetal cardiac irregularity which apparently recovered. No action undertaken until another 24 hours had elapsed when, after a further heavy loss, the foetal heart sounds disappeared. EUA showed a Type II placenta praevia and artificial rupture of the membranes was followed by the delivery of a stillborn infant weighing 4 pounds 10 ounces.

Case 4. 51N/1088

Heavy loss before admission at 34 weeks by dates. Foetal heart satisfactory. Further severe bleeding 6 hours later but foetal heart still satisfactory. EUA three hours later still at the onset of labour showed a Type III placenta praevia and foetal heart no longer heard. A.R.M. performed. Stillborn infant weighing 6 pounds 10 ounces.

Case 5. 51N/3192

Persistent loss for 48 hours following admission at 36 weeks. Foetal heart normal. EUA showed a Type III placenta praevia. Section not done because of maternal bronchiectasis. This was a mistake since the bronchiectasis was a contra-indication to the anaesthetic—which had already been given. Stillborn infant weighing 5 pounds 9 ounces.

Case 6. 53N/81

Persistent loss over 12 hours following 2 weeks conservative management necessitated transfusion. Increased by onset of labour. No interference for further 4 hours when EUA showed a Type III placenta praevia and the cervix almost fully dilated. Infant stillborn and weighed 4 pounds 3 ounces.

Case 7. 54N/1207

Considerable and persistent loss with irregularity of the foetal heart for three hours following admission. EUA showed Type I placenta praevia. Artificial rupture of the membranes was followed by a five-hour labour and the neonatal death of an infant weighing 4 pounds.

Case 8. 56N/1757

This case was similar to Case 4 in that a mistake in maturity was made, the patient being thought to be 34 weeks by dates. The X-ray was also misleading in that a Type I or II was reported, whereas EUA (after 24 hours of persistent haemorrhage) showed a Type IV. The infant delivered by section weighed 6 pounds 9 ounces and died 48 hours later.

Consideration of all these cases shows that the factors which persistently militate against the infant's chances of survival are four in number:

(1) Pregnancy of less than about 34-weeks duration.
(2) Maternal haemorrhage severe enough to warrant transfusion.
(3) Interference or delay by the doctor before admission.
(4) Persistent haemorrhage in cases of reasonable maturity (34 weeks or later) which fails to settle within a few hours of admission and which may lead to unwarranted delay in treatment.

The first two are more or less unavoidable, the third is completely avoidable. Close attention

to the fourth factor and the avoidance of undue delay seem to be the most promising avenues leading to increased foetal salvage.

The X-ray Diagnosis of Placenta Praevia

Since 1951 extensive use of radiology has been made as an aid to diagnosis so that it is worth enquiring briefly into the value of the procedure. From 1951–1952 to 1956–1957 inclusive there have been 169 proven cases of placenta praevia and X-ray help in the diagnosis has been sought in 112 of these. This includes all the cases treated conservatively (i.e., 6 days or more in hospital before delivery) in those years. The cases not X-rayed were those where haemorrhage necessitated active intervention without waiting for X-rays or the clinical diagnosis was so clear that radiology was deemed unnecessary. Radiology was also used in a great number of cases of antepartum haemorrhage which were either not proven cases of placenta praevia or due to other causes. These other cases are not considered here so the figures about to be quoted are probably only a conservative indication of the accuracy of the method. At the same time they will also not indicate the number of false positive radiological diagnoses.

In 95 cases the X-ray diagnosis was correct or substantially so as revealed by subsequent findings at EUA or Caesarean section. In 9 the X-ray was regarded as being either unassessable or unreliable and in a further 8 the report was either wrong or misleading. In this latter 8 was only one case (Case No. 8 above) where the report might have deleteriously affected the infant's chances of survival—by leading to greater delay than was warranted.

These last 8 cases where the report was judged wrong or misleading were subsequently reviewed with the 3 radiologists concerned. In 7 of them it was unanimously decided that it was the man and his experience of the method and not the method itself which was at fault. In the remaining case the radiological findings of anterior placenta praevia of moderate degree (Type I to II) were obviously correct on reviewing the film even to the eyes of a non-radiologist. Yet the findings at EUA and Caesarean section were quite unequivocally those of Type II posterior placenta praevia. If the method is to be accepted as reliable, and the figures given (i.e., an accuracy of at least 85 per cent, for only proven cases of placenta praevia are considered) indicate this is so, this case can only be explained on the basis of a mix-up of patients or their X-rays. If cases other than placenta praevia and those placenta praevias unconfirmed clinically but demonstrated radiologically were considered as well as the proven cases the accuracy would probably be well over 90 per cent and comparable with those quoted by Watson *et al.* (1957).

One thing which has arisen from the consideration of radiology in the diagnosis of placenta praevia is that the radiologist often has much difficulty in deciding what degree of praevia exists. It is felt that the classification at present in vogue (Type I to IV) is too fine a subdivision. This is not a difficulty confined to radiologists alone of course. In the flurry of cutting through or pushing aside a placenta to get the cord clamped and the baby delivered before it becomes anaemic (Butler and Martin, 1954), the average obstetrician may not give much attention to the degree of placenta praevia and when asked afterwards will often be uncertain whether it was Type II or III or even IV. Also a Type I (which may give rise to quite severe haemorrhage) is not easily felt sometimes by vaginal examination. One which, with the patient not in labour, does not quite reach the level of the internal os by an inch or so and is therefore by definition a Type I, may after some hours in labour become quite definitely a Type II when the lower segment is well retracted. Experience with a recent case in this hospital proves this. The case was diagnosed as a Type I by EUA before the onset of labour; with the cervix approaching full dilatation a further vaginal examination (for possible forceps delivery) showed that clearly it was a Type II.

Our own radiologists (Dr. A. F. Crick and Dr. J. H. Stewart) have resorted to a simpler classification in reporting the presence of placenta praevia:

(1) Minor (Type I).
(2) Moderate (Type I to II).
(3) Major (Type III to IV).

We think this is a much more practical classification especially since it is more in line with treatment, i.e., most of the "minor" cases can be delivered vaginally, a proportion of the "moderate" cases will require Caesarean section, whilst all the "major" cases should be delivered abdominally. It is felt that a return to the older classification of marginal, lateral and central placenta praevia (which is what the above classification is, in effect) could be made with advantage.

Discussion

The management and results of treating a series of 242 cases of placenta praevia over a 9-year period (April, 1948 to March, 1957, inclusive) have been reviewed. Because of the diagnostic criteria used it does not include all cases of placenta praevia seen and treated in that time. At least 61 cases which possibly were exampies of placenta praevia have been excluded. Several considerations are worthy of final discussion.

(*a*) The conservative approach to the problem of haemorrhage due to placenta praevia, as first definitely propounded by Macafee, undoubtedly gives results as regard maternal and foetal loss much superior to those obtained with the older viewpoint that the condition is an obstetrical emergency. Especially is this so when it is combined with a high Caesarean section rate as regards actual treatment.

(*b*) Conservatism must not be carried too far or babies will be lost unnecessarily. Where haemorrhage fails to settle within a few hours of admission to hospital an attempt to delay intervention because of infant maturity is unlikely to succeed. Because of the availability of blood transfusion and operating theatre facilities the safety of the mother is unlikely to be jeopardized but that of the infant is. The 8 cases summarized above seem to indicate this quite definitely. If haemorrhage is still present after 10 to 12 hours and the infant is of reasonable maturity, i.e., 33–34 weeks onwards, its chances of survival, even though premature, are higher if Caesarean section is undertaken without further delay. Only in the presence of extreme prematurity does it seem justifiable to temporize in the face of severe or oft-repeated haemorrhage.

(*c*) Is examination under anaesthesia to confirm a clinical and/or radiological diagnosis of placenta praevia always necessary? Experience suggests that it is not and may in fact be most undesirable on occasions. We agree with Watson *et al.* that radiology in this condition is now extremely reliable, so much so that the combination of positive clinical and radiological findings seems sufficient justification for elective Caesarean section where a major degree of placenta praevia has been diagnosed. This policy has come to be accepted as a result of the experience gained in the series, and only when the degree of praevia is thought to be so minor as to justify artificial rupture of the membranes and vaginal delivery, or where clinical and radiological findings are at variance, is vaginal examination in the operating theatre performed. Only twice has this led to possibly unnecessary sections—in both cases, clinically and radiologically, the patient had a major degree of placenta praevia but the sections performed revealed Type I posterior placenta praevia. Despite great care and gentleness vaginal examination sometimes provokes alarming haemorrhage, even in Type I cases, so that it is difficult to justify it where there is good clinical and radiological evidence that a severe degree of placenta praevia exists. The essential thing is to take a balanced view of both clinical and radiological findings and act accordingly. By so doing we do not, as Mills (1957) suggests that Watson *et al.* do, i.e., "decry the value of the traditional examination under anaesthesia" but only wish to remark that it is unnecessary in a fair number of cases.

(*d*) There can be considerable difficulty in distinguishing between some degrees of placenta praevia, especially between Types III and IV. As Grant says, there is much to be said for combining the latter into one group. Logically this means, as suggested previously, a return to the marginal, lateral and central classification.

(*e*) Good results, i.e., zero maternal and low perinatal mortality, in placenta praevia can only be obtained, and maintained or improved, by early diagnosis, late interference, adequate preparation for dealing with sudden or persistent haemorrhage, high Caesarean section rate and the possession of facilities for handling a fair proportion of premature infants.

Acknowledgments

I wish to thank the full and part-time consultants under whose care these patients were admitted, especially Mr. T. R. Plunkett, F.R.C.O.G., who initiated both the principles of management and treatment and the series itself. I acknowledge gratefully the invaluable secretarial assistance of Mrs. E. Port.

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HYDROPS FOETALIS IN ONE OF UNIOVULAR TWINS

BY

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OLDER obstetricians recognized that "generalized dropsy of the foetus", like oedema in the adult, might have many causes. More recently, following the discovery of the Rhesus factor and of an association between haemolytic disease and hydrops foetalis, there has been a tendency to regard foetal dropsy as always being the result of iso-immunization. In fact there is no evidence of incompatibility between foetal and maternal blood in approximately 25 per cent cases (Potter, 1952; Scott, 1958) and in such cases the cause of the hydrops is generally unknown. The following unusual case is described since it may contribute towards an understanding of the mechanism whereby hydrops foetalis is produced.

CASE HISTORY

Mrs. J.S.W., aged 27 years, was first seen in 1958 at the twelfth week of her second pregnancy. The first pregnancy, in 1955, was normal and resulted in the delivery of a healthy male infant weighing 6 pounds 4 ounces. The patient's blood group was "O", Rhesus positive, the Kahn reaction was negative and the haemoglobin level was 90 per cent (Haldane). The urine was normal and the blood pressure 120/50 mm. of mercury. The second pregnancy proceeded smoothly until the seventeenth week when the uterus began to enlarge rapidly. By the twentieth week it became necessary to admit the patient to hospital because of dyspnoea and abdominal pain. By that time the uterus was the size of a 32-weeks pregnancy and the abdominal girth measured 38 inches (95 cm.). Clinically there was evidence of gross hydramnios, and radiography showed the presence of twins. The patient was kept at rest and, for a time, was more comfortable. Indeed, the circumference of the abdomen temporarily decreased by 3 inches (7·5 cm.).

By the twenty-fifth week of gestation the patient again became dyspnoeic and suffered abdominal pain. She had gained 29 pounds (13·1 kg.) in the preceding 13 weeks and showed a moderate degree of generalized oedema. The abdominal girth was 43 inches (110 cm.) and, although the foetal parts were palpable and foetal heart sounds were audible, there was still clear evidence of gross hydramnios. The urine and blood pressure remained normal, the haemoglobin level was 80 per cent and the plasma proteins were 5·8 per cent (micro Kjeldahl), the albumin:globulin ratio being 0·46:1. The chloride (600 mg. per cent), potassium (22 mg. per cent) and sodium (330 mg. per cent) levels in the blood were within normal limits. Neither the oedema nor the hydramnios was significantly improved by rest in bed, a low sodium diet, fluid restriction or by chlorothiazide 1 g. daily, and the blood pressure gradually rose to 130/90. The patient's weight remained constant but the abdomen continued to increase in size and became so uncomfortable that by the twenty-ninth week of pregnancy paracentesis was planned. However, this procedure was forestalled by the spontaneous onset of premature labour.

The membranes ruptured early in labour and a copious but unmeasured amount of straw coloured liquor escaped. A hydropic foetal head (at first thought to be a breech) presented and, because of delay in the second stage of labour, was delivered with forceps. Although the presenting part was at the outlet, and although only moderate force was used, the head was delivered without the foetal trunk. "Spontaneous" decapitation of this kind has been frequently described in cases of hydrops foetalis. Under general anaesthesia the trunk was easily delivered and this was immediately followed by the placenta. Thereafter came the second foetus, still enclosed in its amniotic sac which contained only a normal amount of liquor. The hydramnios had clearly affected only the sac of the first (hydropic) foetus. The second foetus looked normal and its heart continued to beat feebly for a short time after birth.

The mother's subsequent progress was uneventful and further investigation of her blood failed to reveal any antibodies except weak anti-A and anti-B haemolysins. Her husband's blood group was "A" Rhesus positive.

Examination of the Foetuses and Secundines

The first twin was a male, weighing 5 pounds 3 ounces (2,355 g.) and was grossly oedematous. The pericardium and pleurae were covered with petechial haemorrhages. The pericardial and pleural cavities contained moderate amounts of clear fluid and the peritoneal cavity contained a large quantity of greenish-yellow fluid. All the organs were developed normally for the period of gestation. On section, the liver showed a normal haemopoietic pattern.

There were no signs of maceration and, judging by the fact that the amount of liquor in the amniotic sac continued to increase up to the onset of labour, it is probable that the foetus was alive until a short time before birth (Mills, 1949).

The second twin, also male, weighed 1 pound 12 ounces (795 g.), and was in all respects normally developed for the period of gestation. The only significant finding at autopsy was generalized petechial haemorrhages, suggesting intra-uterine asphyxia. The liver was normal both macroscopically and microscopically.

Radiological study of the skeletons showed that the development of centres of ossification, and the lengths of the long bones, were the same in the two foetuses (Fig. 1). The fact that the spine of the hydropic foetus was slightly longer than that of its brother is almost certainly explained by oedema of the intervertebral discs. Indeed, it is probable that the gross difference in weight of the two babies is entirely accounted for by oedema.

The placenta was single and weighed 2 pounds (908 g.). The area serving the hydropic foetus was pale and swollen; that serving the second foetus looked normal. The arrangement of the placenta and membranes was indicative of uniovular twinning. Both superficial and deep anastomoses between the two foetal circulations could be demonstrated and there was no interposing chorion between the two amniotic sacs. It was not possible to determine by naked eye or microscopic examination whether the communications were arterial or venous but it was possible to demonstrate by dissection that, in addition to major vascular anastomoses, certain chorionic villi received vessels from both foetuses.

The two parts of the placenta differed histologically. That associated with the normal foetus (Fig. 2) consisted of villi which, except for occasional hydropic changes, had an appearance normal for the particular stage of pregnancy. The hydropic foetus, however, was related to placental tissue which consisted of villi which were either hydropic or which showed hyperplasia of the stromal core (Fig. 3). Persistence or regeneration of Langhans' layer, commonly seen in the hydropic placenta (Scott, 1958), was not a noticeable feature.

The Cause of Hydrops Foetalis

(1) *Maternal Factors*

Iso-immunization as a cause of the hydrops foetalis is, in this case, virtually excluded by the haematological findings and by the absence of any evidence of red cell destruction or excessive erythropoiesis in either foetus. Indeed, any undetected antibody or any toxic agent in the maternal circulation is unlikely to have caused the hydropic change in one foetus alone. Even if a difference in permeability of the two parts of the placenta is supposed, the anastomoses between the foetal circulations were sufficient to make it likely that any adverse maternal factor would have been distributed to both babies. By the same argument it is unlikely that the maternal hypoproteinaemia was a cause of the hydropic change.

The low level of the maternal plasma albumin nevertheless requires consideration. It might be considered normal for this stage of pregnancy but also it is necessary to consider whether the deficiency was caused by loss of protein into the large pool of liquor amnii or into the hydropic foetus and placenta.

(2) *Foetal Factors*

Generalized dropsy of the foetus associated with iso-immunization is probably the result of cardiac failure secondary to the haemolytic anaemia.

The possibility of foetal heart failure causing hydrops foetalis in circumstances other than iso-immunization is also worthy of consideration. Many cases of hydrops associated with foetal

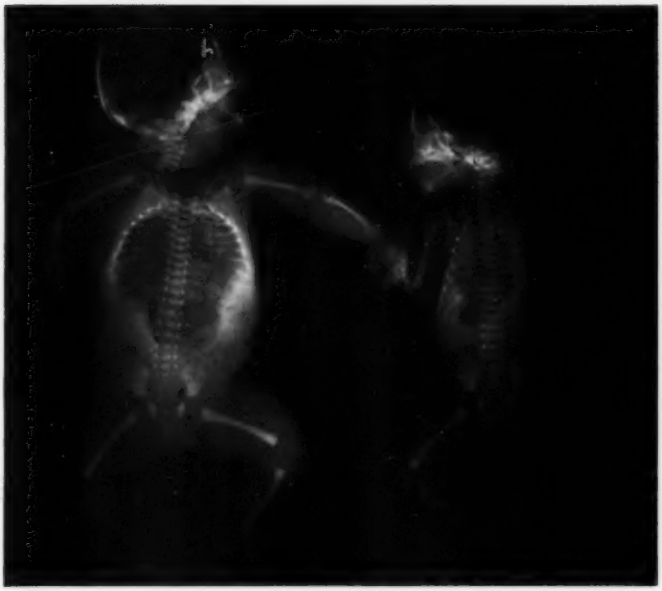

FIG. 1

Uniovular twins—post-mortem X-ray.

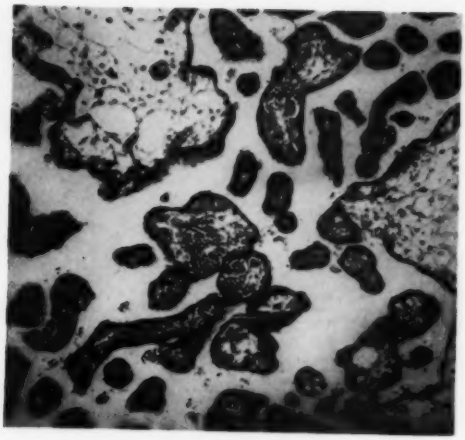

FIG. 2

Area of placenta associated with the normal foetus. ×70.

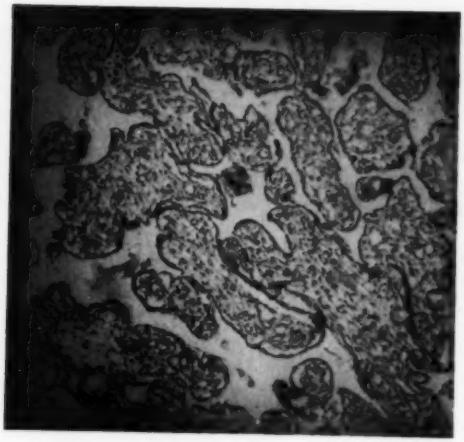

FIG. 3

Area of placenta associated with the hydropic foetus. ×70.

malformation are recorded (Potter, 1952). In these there may be obvious cardiac defects but sometimes the malformation is one which only indirectly interferes with cardiac function. Examples of this are large diaphragmatic herniae and intra-thoracic tumours. A case of the latter causing foetal oedema was described by Seyffert (1920) and another has occurred recently in our own unit.

Ballantyne was especially interested in hydropic changes affecting one of twins and he, like subsequent writers, noted that the twins in such cases were frequently uniovular and that the affected foetus was often abnormal. The best example is the acardiac monster, which almost invariably shows generalized oedema of its tissues (Ballantyne, 1898; Capon, 1922). In this circumstance there is clear evidence of cardiac deficiency in the affected foetus. Even when neither foetus is grossly abnormal, the intercommunication of the circulations *via* placental anastomoses always raises the question of one foetal heart over-riding the action of the other (Browne, 1951), and causing relative cardiac decompensation. This concept is generally put forward to explain the hydramnios sometimes found in one sac of uniovular twins. It is then argued that the kidneys of the dominant or "favoured" foetus, having a better blood supply, secrete for both foetuses to cause the hydramnios in the sac of the normal, or stronger, foetus. In the case recorded here, however, it is to be noted that the excessive amount of liquor was around the affected foetus, the one in which, on the above theory, there would have been cardiac insufficiency.

Newman (1923) showed that 5 to 10 per cent of the blood entering the placenta from one uniovular twin may return in the umbilical vein of the other twin. Such a transfer would not be likely to impose too great a burden on one foetal heart but, if the drain were continuous, exsanguination and early death of the "unfavoured" foetus would result. The nature of the vascular connexions (e.g., whether they are arteriovenous) must be important in deciding the ultimate outcome in each case.

There is little doubt that the occurrence of foetal cardiac failure by any mechanism could cause generalized oedema of the foetus. The generalized distribution of the oedema in the foetus does not exclude a cardiac origin. The circumstances of the foetus *in utero* are such that none of its parts can be regarded as especially "dependent" and therefore attracting a disproportionate amount of fluid.

The chief excretory organ of the foetus is the placenta, so hydrops is unlikely to arise from renal failure. Indeed, the foetus suffering from renal agenesis or complete obstruction of the lower urinary tract does not become oedematous, nor, as judged by the study of its blood electrolytes, does it suffer any gross metabolic upset (Jeffcoate and Scott, 1959). A foetal renal mechanism for hydropic change can therefore be dismissed unless one regards the placenta as functioning as an extra-corporeal kidney.

(3) *Placental Factors*

In this, as in all cases of hydrops foetalis, the placenta showed gross macroscopic and microscopic variations from the normal. The characteristic changes of avascularity and oedema with overgrowth of the stroma of the villi were well demonstrated, but the re-growth of Langhans' layer which is also described was not observed in this case. With this possible exception, the changes in that part of the placenta supplying the hydropic twin were in this case typical. Are they to be regarded as secondary to the changes taking place in the foetus or are they part of the primary disease complex?

The variety of the aetiological factors associated with hydrops foetalis suggests that the placental changes are often secondary. Nevertheless, in certain cases at least, they may be primary and, by disturbing placental exchanges of fluid, nutriments and metabolites, might cause foetal oedema. Capon (1922) considered that a primary placental change increased the resistance in the peripheral foetal circulation, and that this led to cardiac hypertrophy followed by cardiac failure.

In the case under discussion neither foetus showed evidence of cardiac or renal hypertrophy and the physical development of the foetus which might be presumed to have an unsatisfactory placental function was equal in all respects to that of its brother.

Unfavourable placentation, or some other circumstance determining a nutritional defect in early embryonic life, might be postulated by analogy with animal experiments which have shown that disturbance of the embryonic environment of chicks (Dareste, quoted by Ballantyne), and high altitude anoxia in mice (Prindle, Ingalls and Kirkwood, 1955) can cause foetal malformations, hydramnios and even hydropic changes in the placenta and membranes. Observation of the process of one-egg-twinning in the armadillo and experiments with starfish suggest that any agent which slows down early development of the embryo may result in twinning (Newman, 1942). In humans, the very occurrence of twins is an atavistic trait, and suggests a possible variation from the normal constitution or environment. It is therefore important to recall that, even in the "normal" part of the placenta, some villi were found to be hydropic. This may mean that the adverse factor did operate over the whole placenta area but in different degrees, so that only one foetus showed obvious pathological changes. If this is accepted then it is necessary to re-entertain the possibility of a genetically determined lesion, or of some factor adversely affecting placentation and subsequent embryonic environment.

The Cause of Hydramnios

A further aspect of this case which is of interest, although it appears to complicate rather than clarify the issue, is the gross hydramnios affecting the sac of the hydropic foetus. Hydramnios can complicate hydrops foetalis of any aetiology. The degree of hydrops in such cases is usually severe and the hydramnios may be easily explained by gross oedema of the lips, mouth and fauces which makes it impossible for the foetus to swallow liquor amnii (Scott and Wilson, 1957). One reason for hesitating to accept this simple explanation in this case is the fact that the hydramnios appeared so early in pregnancy—prior to the time at which foetal deglutition usually plays a significant part in the control of the volume of liquor amnii (Jeffcoate and Scott, 1959).

If the hydramnios is presumed, as suggested by Browne, to be the result of polyuria in the foetus with the dominant vascular apparatus—then it follows that it was the hydropic foetus which was dominant and the normal foetus which should have suffered cardiac failure.

One theory of the aetiology of hydramnios put forward early in this century, revised and developed by McInroy and Kelsey (1954), and recently discussed by Jeffcoate and Scott (1959) is that it can be the result of foetal polyuria which occurs when placental function is defective. If the placenta fails as an excretory organ, it is argued, metabolites collect in the foetus and stimulate its kidneys to secrete an excessive amount of urine. This concept, hypothetical as it is, is in keeping with the suggestion of a primary placental error in this case and could then explain both the hydrops foetalis and the hydramnios.

Conclusion

The most important conclusion is confirmation of the fact that hydrops foetalis need not be maternal in origin. The placental changes must be regarded at least as an integral part of the disease and not merely the consequence of foetal oedema, and by a process of exclusion it seems possible that the placenta may have initiated the changes in the foetus.

It is hoped that the details of this case may be of value when future study of the subject is undertaken. Only then can an explanation of the happenings be expected.

I am indebted to Professor T. N. A. Jeffcoate for permission to publish this case and for his helpful criticism and advice in the preparation of the paper.

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HISTOPATHOLOGY OF STRIAE GRAVIDARUM

BY

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INTRODUCTION

PRIOR to Küstner (1876) changes in the Rete Malpighii were thought responsible for the lesions and it was he who first placed them at a deeper level. The elastic fibres were considered to be at fault by Troisier and Menetrier (1889), Unna (1896), Allbutt (1899), Macleod (1903, 1933), Lever (1949), Crofts and Macrae-Gibson (1950), and Wiener (1955). Unna suggested an altered morphology in the elastic fibres while Hurford and Snell (1943), stating that they showed ". . . no obvious disease", suggested fragmentation of the collagen bundles. Spirito (1946) even suggested that changes in the elastic tissue layer bore no relation to the actual stria.

The multiplicity of published views regarding histopathological changes responsible for striae gravidarum is interesting although even more so is the fact that none of them were supported by any convincing evidence. Crofts and Macrae-Gibson admit their view was based on one biopsy examination. A thorough search has failed to provide one illustration showing the detailed changes in skin striae. The great majority of modern obstetric textbooks persist in the view that stretching causes rupture of the elastic tissue fibres which as a result are not found under the stria but rather all curled up at the edge. Because of this I wish to report the results of my study.

BIOPSY METHOD

Many women during pregnancy gave their consent for the removal of complete striae under local anaesthesia. Experience showed that the stria in its full length, breadth and depth should be removed completely together with a small area of surrounding skin. In this way changes may be studied as the normal skin is followed into the striae skin. In order that the tissues for examination would be protected from disturbance by the local infiltration of anaesthetic fluid the area to be excised was blocked off in a circumferential manner rather than directly infiltrated.

Striae were removed from various situations such as the breast, abdominal wall and thigh at various stages of the pregnancy. Some were taken before the 20th week whilst others were excised at all stages onwards even up to removal at Caesarean section at term. The changes to be described apply equally to those removed early or late and from the different situations. Vascular changes could not be demonstrated because a technique could not be evolved for injecting the vessels of a small localized area.

Immediately following excision the skin was gently laid out and pinned to a flat piece of cork and put into 10 per cent formalin. Most sections were cut at 8 μ thickness. The sections were usually taken at right angles through the central area so that each stria was then flanked by a piece of normal skin. Haematoxylin and eosin, Verhoeff, Orcein and Van Gieson stains were used.

FINDINGS

The thickness of each stria was about half that of the adjacent skin.

Epidermis

In the normal skin adjacent to a stria the epidermis was about 6 to 10 cells in thickness, normally ridged on the external surface and

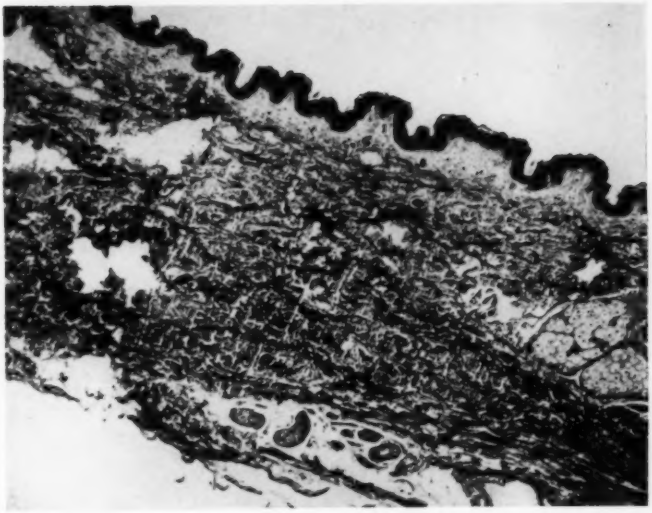

FIG. 1

Section of skin adjacent to stria. Normal epidermal layer with Rete Malpighii. × approx. 40 (Verhoeff).

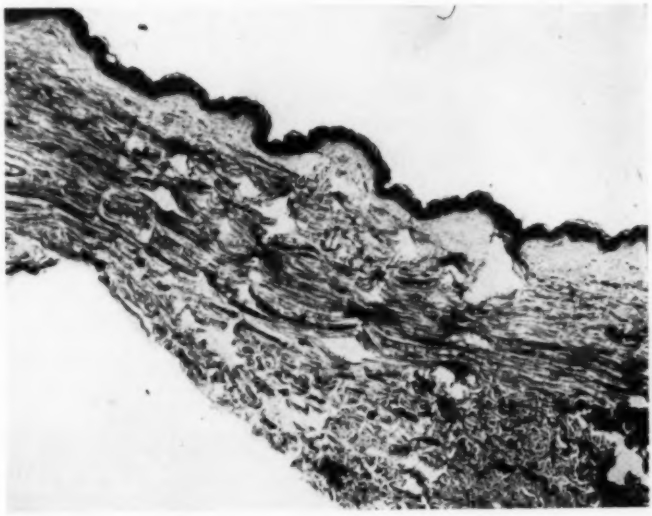

FIG. 2

Same section as Fig. 1. Skin of stria; note abundant elastic fibres pulled longitudinally. × approx. 40 (Verhoeff).

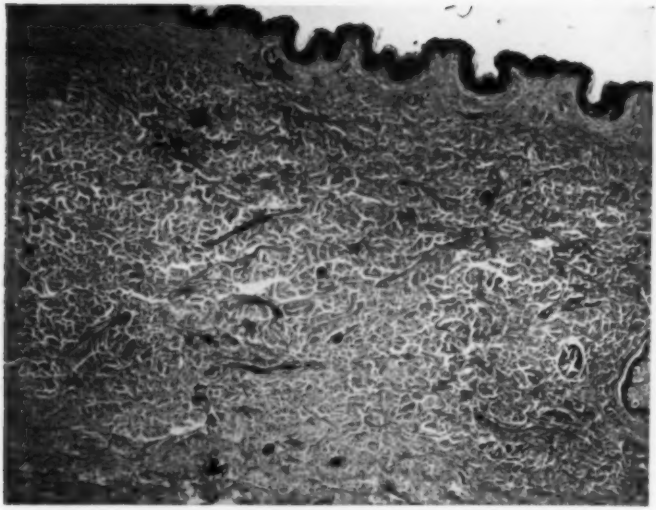

FIG. 3

Collagen bundles of skin adjacent to stria showing criss-cross arrangement. × approx. 40 (H. and E.).

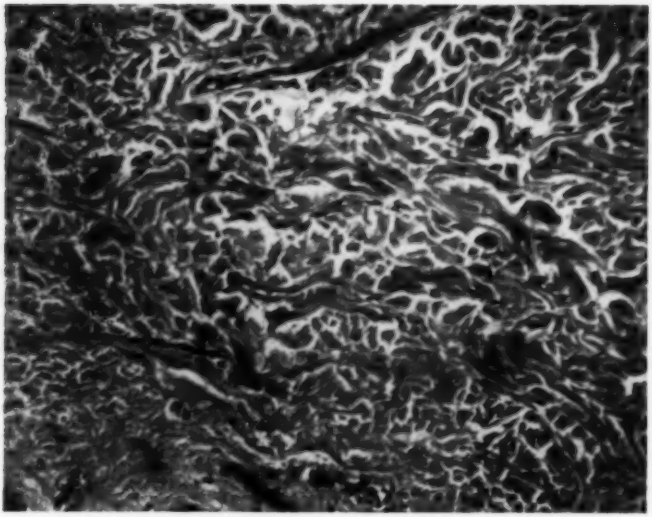

FIG. 4

Same section as Figure 3. × approx. 110 (H. and E.).

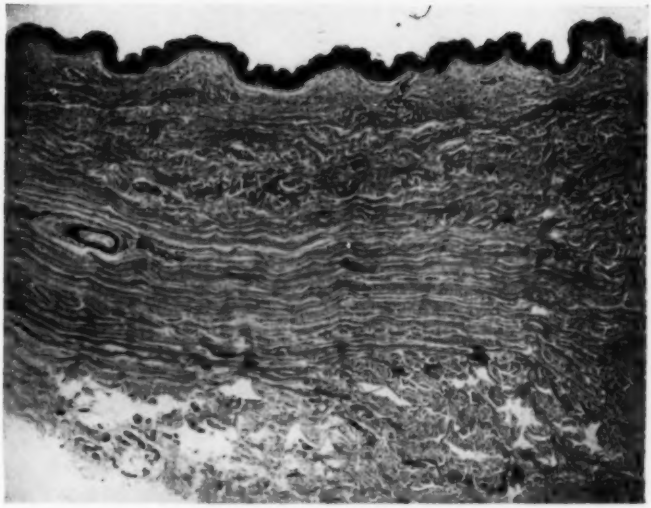

FIG. 5

Skin of stria, same section as Figure 3. Note collagen bundles pulled longitudinally giving impression of tension. At right side of picture the change over from normal skin to stria skin is seen. (H. and E.)

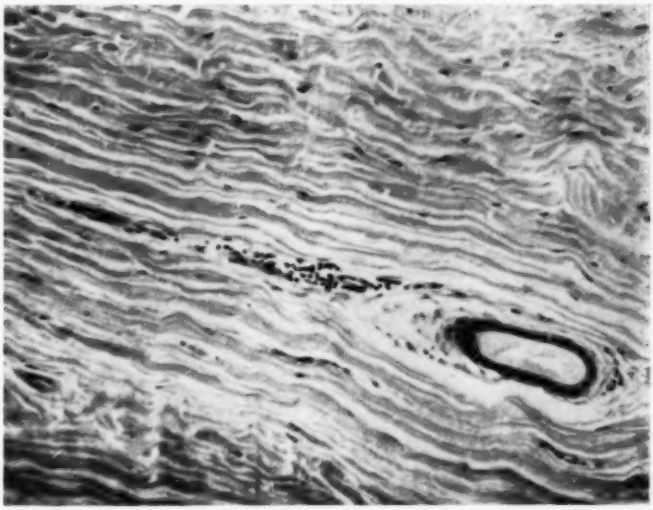

FIG. 6

Same section as Figure 5; showing collagen bundles. × approx. 110 (H. and E.).

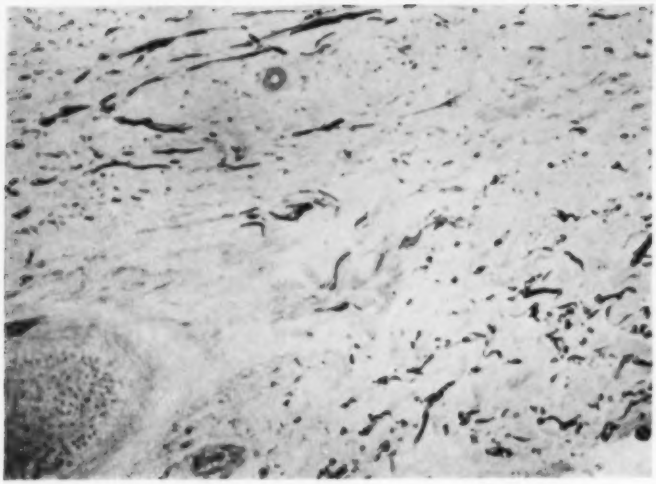

FIG. 7

Elastic tissue of skin adjacent to stria. × approx. 110 (Orcein).

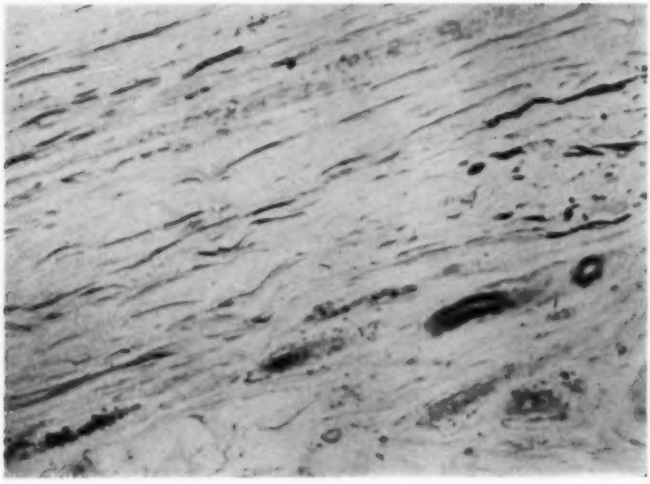

FIG. 8

Same section as Figure 7—elastic tissue under stria. (Orcein).

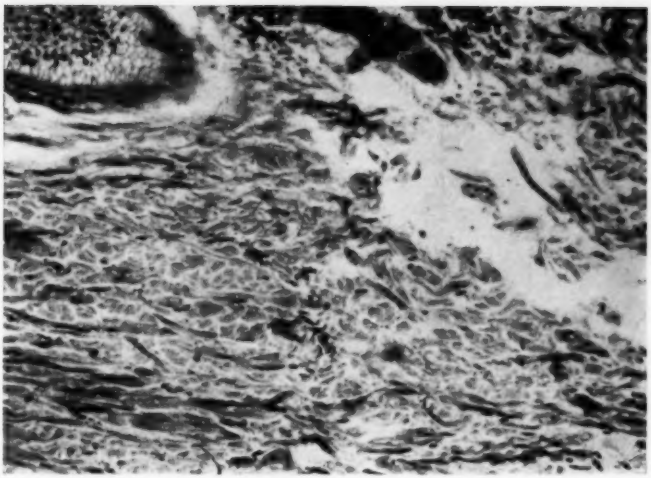

FIG. 9
Skin adjacent to stria; × approx. 110 (H. and E.).

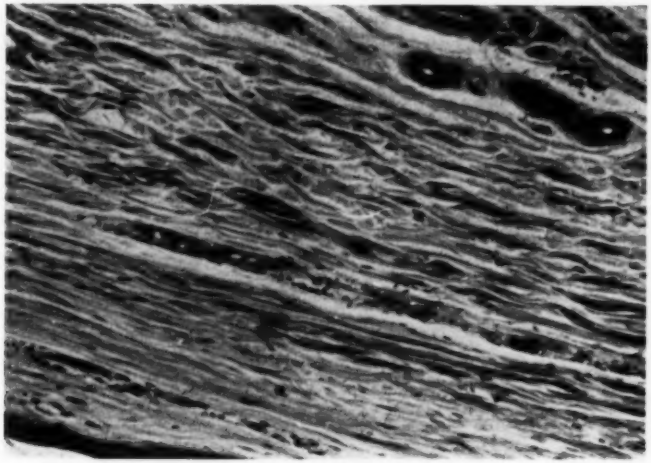

FIG. 10
Same section—skin under stria. (H. and E.).

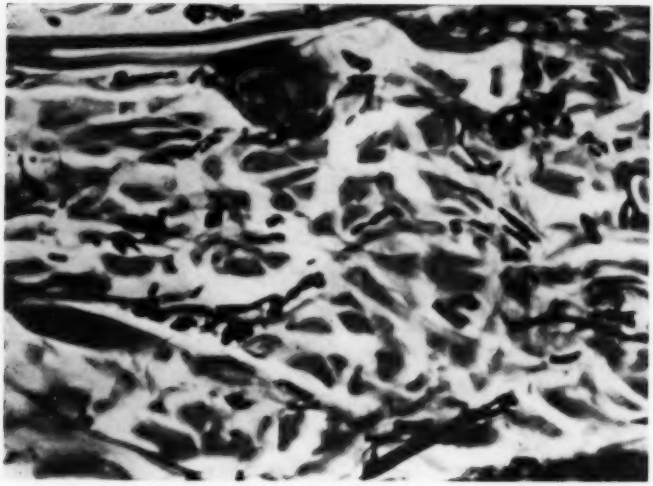

FIG. 11

Elastic tissue of normal skin. × approx. 500 (Verhoeff, counter-stained with Eosin).

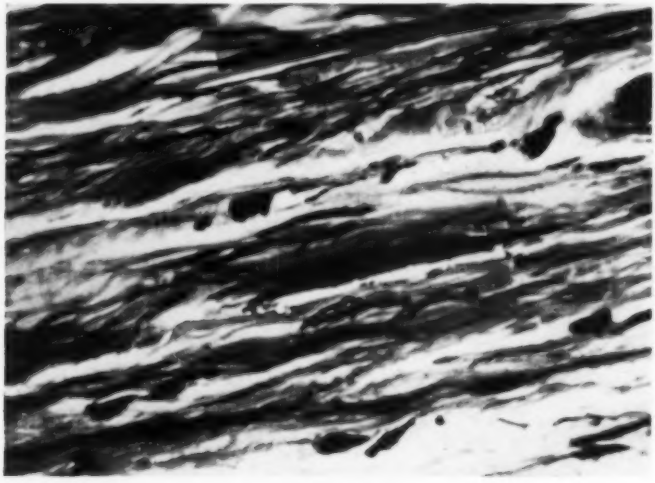

FIG. 12

Same section—elastic tissue of stria skin. (Verhoeff, counter-stained with Eosin.)

FIG. 13

Elastic fibres under stria—note beading in some fibres. × approx. 580 (Verhoeff).

FIG. 14

Elastic fibres under stria—note beading in some fibres. × approx. 580 (Verhoeff).

showing normal Rete Malpighii (Fig. 1). As the epidermis was traced along into the stria it was found to become thinner, smoother on its external surface with less pronouncement of underlying Rete Malpighii (Fig. 2).

The Collagen

Under the normal skin adjacent to a stria collagen bundles could constantly be noted as running in various directions producing a criss-cross appearance (Figs. 3, 4). As the stria area was approached the bundles gave the appearance of being rearranged mainly in a longitudinal direction (Figs. 5, 6). An actual change over area is well seen in Figure 5. No evidence was seen of disruption of collagen.

The Elastic Tissue

Elastic tissue fibres in the skin adjacent to a stria were arranged in infinite ways as is customary in normal skin (Figs. 7, 9, 11). In strict contrast, under the stria itself, they were always noted as straightened out longitudinally as though under tension (Figs. 8, 10, 12). There was no evidence found for the suggestion that they became torn and retracted in a coiled up fashion to the edge of the stria. A close look at Figure 11 with the darkly staining elastic fibres shows them to adopt all shapes and thicknesses while in Figure 12 the fibres have completely changed by being thinner, straightened out longitudinally and show paler staining. Focussing showed these fibres to lie in many different planes although still thinned and lying mostly longitudinally. A few of the elastic fibres exhibited a beading or fine chain effect which was particularly well seen by focussing (Figs. 13, 14).

Discussion

The three main elements, epidermis, collagen and elastic fibres have been shown to remain intact in the stria although each gave the impression of being stretched and under tension. No support could be found for the accepted views of disruption of any of the three main elements.

One cannot escape the suggestion that the ground substance matrix has changed in some way and lost its holding power and its ability to maintain the tissue elements in the same relationship with one another. This would then result in these elements being left in some way unsupported and yet responsible for the maintenance and integrity of the skin. Stretching would appear to be, therefore, their only way of discharging this responsibility.

Maximow and Bloom (1957) mentioned the varying viscosity of the fluid or gel-like ground substance and how it was influenced by age, activity and certain pathological conditions. These authors pointed out that collagen fibres were very resistant to a pulling force and required several hundred Kg./cm.^{2} before they ruptured. With this force their elongation was only 15 per cent. The elastic tissue on the other hand would stretch by 150 per cent before rupturing. Thus from their work it must be concluded that the elastic tissue fibres would be protected from rupturing by the very resistant collagen. This great extensibility of elastic tissue has been reported by others (Meyer and Ferri, 1937).

Better staining techniques than are at present available or possibly entirely different methods altogether, will be required to demonstrate ground substance changes in the actual striae areas. Steiner (1957), from his electron microscopic studies, pointed out the increasing complexity of ground substance investigations and stated that quantitative changes were not demonstrable histochemically. Meyer (1953) had previously suggested they were.

These tissue studies were conducted as one section of an extensive clinical study searching for relationships between adrenal cortical hyperactivity and striae gravidarum. This work has left little doubt that ketogenic steroid activity plays the major role in striae formation and not stretch as was formerly accepted.

Summary

(1) The evolution of present-day views on the tissue changes in striae gravidarum is briefly outlined.

(2) Today there is general acceptance of an elastic tissue failure.

(3) Recent studies dispute this.

(4) No evidence of tearing and retraction of elastic fibres from the skin of striae was found.

(5) The evidence suggests that striae gravidarum result from ground substance changes which permit a rearrangement rather than a tearing of either the collagen or elastic tissues.

(6) Associated studies suggest a close relationship between striae gravidarum and adrenal cortical hyperactivity.

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THE PROGNOSIS FOR THE FOETUS OF MOTHERS OF FORTY YEARS OF AGE AND OVER

BY

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IT is well known that "increasing maternal age enhances the hazard to the foetus" (*Lancet*, 1954), but there are few figures to show the exact extent of this hazard. In the investigation reported here, the case records were studied of infants born to mothers of forty years old or over, who were delivered in the Jessop Hospital for Women, Sheffield, during the years 1952–1956 inclusive. This hospital takes mainly abnormal maternity cases, and the figures given cannot be taken as necessarily representative of the general population. Also the fact that the mother was over 40 years of age was, of course, known to the obstetricians, and the management of the case may have been modified on that account. The length of the follow-up period varied from 10 days to a year, depending on many factors, the most important being the clinical condition of the baby and the distance the mother lived from the hospital. No attempt was made to recall the children for special observation.

Table I shows the total number of foetuses under consideration. Out of a total of 8,646 pregnancies, 358 were stillborn and will be considered later. This leaves 8,288 liveborn children. Of these 255 were born to mothers of forty years old or over. One hundred and ninety-two of the 8,288 children subsequently died in hospital. Seven out of the 255 children of older mothers died, giving a death rate of 27·4 per 1,000, and 185 out of 8,033 children of mothers below 40 also died, giving a death rate of 23·1 per 1,000. These figures cannot strictly be called the neonatal death rate, since a few of the children were not followed up for a month. However, many children were followed for a month or more, and in this group no deaths occurred between the 5th and 30th day. As all children were followed until at least the tenth day, it is probable that the true neonatal death rate would closely resemble the figures given. In Table II the figures have been broken down to separate the mature from the premature babies. As would be expected, the death rate for the premature babies (which included several infants under 2 pounds) is far higher than that for mature babies. Again the risk for the

TABLE I

Total Number of Babies Considered in this Investigation

1952–1956 Inclusive	Age of Mother		Total
	Under 40	40 or Over	
Total live births	8,033	255	8,288
Died in hospital	185 (23·1)	7 (27·4)	192
Stillbirths ..	342 (40·8)	16 (59·0)	358
Total pregnancies	8,375	271	8,646

The figures in ( ) are the rate per 1,000 live births for children who died in hospital, and per 1,000 live and dead for the stillbirths.

TABLE II

Death Rate

	Death Rate 1,000 Live Births		
	Mature	Premature	Total
Babies of mothers under forty ..	4·97 (36)	186 (149)	23·1 (185)
Babies of mothers forty or over ..	8·51 (2)	250 (5)	27·4 (7)

The figures in ( ) are the total number of children concerned.

TABLE III
Outcome of Pregnancies by Ages

	Ages								
	40–	41–	42–	43–	44–	45–	46–	47–	48
Children discharged from hospital alive ..	86	57	35	34	20	6	7	1	1
Died in hospital*	2 (22)	—	1	2	—	–	–	–	1
Stillbirths†	5 (54)	1 (17)	2	2	4	–	2	–	–
Total pregnancies‡	93	58	38	38	24	6	9	1	2

* Figures in ( ) is death rate per 1,000 live births.
† Figures in ( ) is number of stillbirths per 1,000 births dead or alive.
‡ One mother's age was unknown.

children of mothers over forty is greater than for the babies of younger women, but perhaps not so great as might have been expected.

The question arises as to whether older mothers are more likely to give birth to premature babies. This might be anticipated on empirical grounds, as the incidence of multiple births is higher in older women (*Lancet*, 1954) and toxaemia of pregnancy, with resulting prematurity of the infant, is especially a disease of the old and young mother (Stanton, 1956). This investigation however does not really support the supposition. There were 800 premature babies in 8,033 live births (9·9 per cent) in the group of mothers under forty years old, compared with 20 out of 255 (7·8 per cent) in the mothers over forty. Bearing in mind the vagaries of selection for hospital confinement, these figures cannot be said to show a significant difference.

The causes of death of the seven children who died in hospital were as follows (with age in parenthesis): gross congenital heart disease (2 days), multiple congenital abnormalities ($\frac{1}{2}$ hour), rhesus incompatibility resulting in hydrops foetalis ($\frac{1}{2}$ hour), placenta praevia (6 hours), mongolism with congenital heart disease (3 days). Two babies of mothers with pre-eclamptic toxaemia died of prematurity (2 and 5 days).

Table III shows the outcome of the pregnancies by ages in the mothers of forty and over. There are three groups: children discharged alive, children dying in hospital and stillbirths. With regard to the mortality rate the figures are too small to show more than a trend. It is apparent on the one hand, that the outlook for the foetus worsens considerably with advancing maternal age. On the other hand a pregnancy even at the age of 48 years old may result in a live child. One of the two children born to mothers of this age was discharged from hospital at the age of one month old perfectly healthy. This of course is by no means a record. Out of a total of nearly 300,000 deliveries in several maternity hospitals in the United States, Stanton (1956) recorded 8 viable births with mothers of 48 years old, and 3 at the age of 49 years old. It must however be remembered that a woman's age is not an accurate scientific measurement.

The stillbirth rate (Table IV) shows that the prognosis is worse for the foetus of a mother of forty years old or above, the figures being 59·0 per 1,000 births for the older age group as against 40·8 for the infants of younger women.

TABLE IV
Stillbirth Rate

	Stillbirth Rate per 1,000 Births Alive or Stillborn		
	Mature	Premature	Total
Babies of mothers under forty ..	18·3 (135)	205 (207)	40·8 (342)
Babies of mothers forty or over ..	24·9 (6)	333 (10)	59·0 (16)

The figures in ( ) are the total number of children concerned.

TABLE V
Parity Table

	Age of Mothers				Total	Per-centage Deaths
	40 and 41	42 and 43	44 and 45	46, 47 and 48		
Group A (first pregnancy)	48 (+1)	21 (+1)	4	0	73 (+2)	2·8
Group B (1, 2 or 3 previous children) ..	67 (+3)	25 (+5)	15 (+1)	3	110 (+9)	8·2
Group C (4, 5 or 6 previous children) ..	19 (+2)	12 (+1)	5 (+1)	4	40 (+4)	10
Group D (7 or more previous children)	7	9 (+1)	2 (+1)	2 (+1)	20 (+3)	75

The figures in ( ) are the number of deaths, both in children born alive and stillbirths.

Table V gives the figures for the parity of the mothers. For ease of analysis four groups have been considered. Group A are mothers in their first pregnancy, group B are mothers who had 1, 2 or 3 previous children (live or stillbirth), group C had 4, 5 or 6 and group D 7 or more. From the table it will be seen that the percentage death rate rises progressively in the four groups, being 2·8, 8·2, 10 and 75 per cent respectively. This does not give the true picture, however, as when group B (1, 2 or 3 previous children) was subdivided, it was found that there were no deaths among the 41 babies born to mothers who had had only one previous child.

An attempt was made to determine whether there was an increased incidence of major congenital abnormalities among the children of older women, but the figures are too small to warrant any conclusion being drawn. There were 3 mongols, 2 children with cleft lips or palate and one with each of the following: congenital heart disease, talipes, spina bifida and multiple abnormalities. It is possible that some abnormalities such as hydrocephalus or congenital heart disease did not manifest themselves during the period of observation. The incidence of mongols in this series (11·4 per 1,000 live births) approximates fairly closely to the figure of 14·8 per 1,000 live births in the much larger series of mothers over 40 years old reported by Carter and MacCarthy (1951).

SUMMARY AND CONCLUSIONS

In a series of 271 pregnancies occurring in mothers of forty years old and over, 7 children died in hospital within the first few days of life. This gives a death rate of 27·4 deaths per 1,000 live births compared with the figure of 23·1 for all other deliveries in the hospital during the same period. The figures for stillbirths were 59·0 and 40·8 per 1,000 births respectively. Considering that the hospital concerned admits mainly difficult and abnormal maternity cases, it will be seen that the chances of a healthy woman of forty or over being delivered of a viable child are nevertheless very high.

Two pregnancies occurred in women of 48. One child died within half an hour with multiple congenital abnormalities, the other child was very well when seen one month after birth.

When the parity of the mother was considered it was found that all but 2 of the deaths occurred among the babies of mothers who had had two or more previous children. The other 2 occurred in first pregnancies. As 73 out of 75 mothers having their first baby over the age of 40 (one mother was 45) had a live child, the evil prognostic significance attached to the phrase "elderly primipara" is perhaps no longer justifiable.

The incidence of mongolism was 11·4 per 1,000 live births, which is similar to another large series of cases. The incidence of other major congenital abnormalities was too small to be of significance.

ACKNOWLEDGMENTS

I would like to thank Dr. T. Colver and Professor R. S. Illingworth for access to the notes of infants under their care. Professor Illingworth suggested the investigation and kindly criticized this paper.

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A CASE OF ACUTE PRIMARY SUPRARENAL HAEMORRHAGE IN PREGNANCY

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CRAWFORD (1951) and MacGillivray (1951) have drawn attention to the occurrence of suprarenal haemorrhage and thrombosis in pregnancy, their studies being based on post-mortem findings. MacGillivray stated that the lesions in some cases did not seem irreparable and that death might now be avoided by the use of recent improvements in adrenocortical hormone therapy. Accurate and early diagnosis may therefore be important and for this reason the following case is reported. Crawford and MacGillivray present adequate surveys of the literature before 1951 and Shearman (1957) of the more recent literature. These are therefore not repeated here. The condition is uncommon in pregnancy. MacGillivray (1951) reported 9 fatal cases from the records of the Glasgow Royal Maternity and Women's Hospital and Shearman (1957) 2 cases occurring in 5 years in the Royal Prince Albert Hospital, Sydney.

CASE REPORT

Mrs. McN., a primigravida aged 26 years, was admitted to Bellshill Maternity Hospital on 9th January, 1957 at 12.30 p.m. in the 36th week of pregnancy. She gave a history of sudden onset of severe upper abdominal pain and continuous vomiting of brown fluid since 2 a.m. of that day. She had attended the hospital antenatal clinic since the fifth month of pregnancy and no abnormality had been recorded.

On examination the patient did not look shocked, the face and mucous membranes being well coloured. There was some slight tenderness and rigidity in the upper abdomen. The uterus was the correct size for the duration of the pregnancy and was quite soft, the foetal parts being easily felt. The foetal heart, however, could not be heard. The temperature was within normal limits. The main clinical finding was a pulse rate of 140 beats per minute with poor volume. The blood pressure was 115/85 and no cardiovascular abnormality could be detected. The urine contained no abnormal constituents. Simple thrombin coagulation test (fibrindex test) as described by Scott (1955) showed good clot formation within 60 seconds. The haemoglobin was 85 per cent (Sahli).

Treatment and Progress

Initially dextrose 5 per cent in normal saline was given by continuous intravenous drip, 1 pint being given in 6 hours, and morphine gr. ¼ by intramuscular injection.

10th January, 1957. The vomiting of brown fluid continued. The pulse rate had risen to 160 beats per minute and the blood pressure had fallen to 95/75 mm. Hg. The extremities were dusky red and congested, but reasonably warm. The peripheral capillary circulation was sluggish but the patient's face was of good colour and she did not have the usual appearance of collapse. After consideration of various possible causes which are mentioned in the discussion (see below), a diagnosis of peripheral circulatory failure due to primary suprarenal deficiency was made and it was decided to treat her with hydrocortisone intravenously, 100 mg. being given over 6 hours in the intravenous fluid. Crystamycin was given prophylactically.

11th January, 1957. Vomiting continued, the vomit still being of brown fluid and the extremities remained congested. The general condition however had improved, the pulse rate having fallen to 120 and the blood pressure having risen to 140/86 mm. Hg. Short irregular uterine contractions were occurring and there was a blood-stained mucoid vaginal discharge. On vaginal examination the cervix was found to be dilated to the size of two

finger-breadths and the forewaters were ruptured to accelerate labour. Meconium stained liquor escaped.

Continuous intragastric suction was now instituted in an attempt to control the vomiting.

Labour progressed quickly and five hours after rupture of the membranes the baby was delivered by forceps under nitrous oxide, oxygen and minimal ether anaesthesia on account of slight delay at the outlet. In addition to the intravenous hydrocortisone, 50 mg. was given by intramuscular injection one hour before the delivery as the pulse rate had risen to 160. The foetus was macerated and weighed 6 pounds 6 ounces. The third stage lasted only a few minutes and bleeding was slight. No evidence of retro-placental clot formation was found. Although the pulse rate rose during delivery the blood pressure remained steady at 110/70 mm. Hg at the end of the third stage.

Two hours after delivery the pulse was so fast as to be uncountable; the extremities were cyanosed, and—for the first time—cold. The blood pressure was 90/55 mm. Hg.

Increasing the rate of intravenous administration of hydrocortisone by 20 drops/minute caused a rise in blood pressure and a fall in pulse rate and any decrease in the rate of flow caused the diastolic blood pressure to fall below 50 mm. Hg with deterioration in the general condition.

12th January, 1957. The patient's condition remained unchanged apart from the development of mild ileus. Hydrocortisone was being given intravenously at the same rate as before (now about 100 mg./4 hours) and in addition 50 mg. cortisone intramuscularly 6-hourly.

13th January, 1957. Thirty-six hours after delivery a definite improvement in the patient's condition was apparent. The extremities became warm and pink. The blood pressure rose to 140/80 mm. Hg and the pulse rate dropped to 120 beats per minute. Intravenous hydrocortisone was stopped but the intramuscular cortisone was continued. The improvement in the patient's condition continued.

14th January, 1957 (3rd day of the puerperium). Improvement was maintained. Intragastric suction was discontinued. Culture of the faeces showed no significant growth.

16th January, 1957 (5th day of the puerperium). The general condition was much improved and there was only occasional vomiting. The pulse rate had now fallen to below 100 beats per minute. Intravenous fluids and crystamycin were discontinued. Cortisone dosage was reduced to 25 mg. daily by mouth.

Thereafter recovery was steady although some diarrhoea and occasional vomiting persisted until the 9th day of the puerperium. Cortisone administration was discontinued on the 7th day.

There was never any gross diminution of the output of urine and biochemical investigations revealed only a mild deficiency of blood sodium and potassium, probably the result of dehydration.

The patient was discharged from hospital on the 19th day of the puerperium and was seen again six weeks after delivery. She was then well and had a blood pressure of 120/80 mm. Hg.

Discussion

This case falls into the group associated with late vomiting of pregnancy. The association between late vomiting and suprarenal haemorrhage has been stressed by both Crawford (1951) and MacGillivray (1951): the latter suggesting that the vomiting may predispose to suprarenal haemorrhage. The sequence of events in our case, however, would indicate that the vomiting was secondary to the suprarenal lesion. An increased liability to rupture of congenital aneurysm during pregnancy in the splenic and renal arteries has been noted by Zummo, Williams and Uzanski (1952) and it is possible that defects in the suprarenal vessels may be the important causal factor in suprarenal haemorrhage. The increased blood volume in pregnancy may be the factor which brings about the rupture in all of these sites. Diddle, O'Connor and Platt (1958) report a case of rupture of a suprarenal vein confirmed at operation associated with concealed accidental haemorrhage of pregnancy.

The differential diagnosis presents considerable difficulty and such conditions as perforated peptic ulcer, biliary colic, acute pancreatitis, appendicitis and intestinal obstruction have to be considered. The minimal tenderness and rigidity in this case were not characteristic of perforated peptic ulcer or biliary colic and the situation of the pain was not typical of appendicitis, even in pregnancy. In acute pancreatitis there is usually collapse and pallor, subnormal temperature and lowered blood pressure with minimal abdominal rigidity and pain deep in each loin. The serum amylase is greatly increased in acute pancreatitis. This test was not performed in this case.

The criteria on which the diagnosis of acute suprarenal failure is based are essentially clinical. The sudden onset, absence of pallor, tachycardia, low blood pressure and poor peripheral circulation with cyanosis of the extremities are the main features. The patient is well orientated and warm and there is not the anxiety and restlessness which accompany shock from blood loss. With the passage of time these latter features develop but initially, when it is important to make an accurate differential diagnosis, they are absent (Shearman, 1957).

Adrenocortical function does not appear to have been entirely suppressed at first as the blood pressure did not fall to an abnormal level until the day after the onset of symptoms. Labour and delivery, however, appear to have exhausted entirely the output of the adrenals. This is in accordance with the observations of Gemzell, Robbe and Ström (1956) on the amount of 17-hydroxycortisteroids in the blood in pregnancy and labour. They found a rise during labour and concluded that this indicated an increased adrenal stimulation due to the systemic stress of labour. It is possible that the placenta may have provided some adrenocortical steroids and that the withdrawal of these following the birth of the placenta may have precipitated the complete collapse which followed delivery; Johnson and Haines (1952) have isolated cortisone-like substances from the placenta.

The principles of adrenocortical hormone therapy in suprarenal failure have been well described in a recent article by Shearman (1957). It would appear that dosage and rate of administration must be governed by the patient's response.

Our experience in the treatment of this case appears to justify the prediction made by MacGillivray (1951) that some adrenal lesions were reversible and that adrenocortical hormone therapy should keep the patient alive long enough to allow the gland to recover its function.

Summary

(1) Attention is drawn to the occurrence of haemorrhage and thrombosis in the suprarenal vessels in pregnancy.

(2) A case of primary suprarenal failure in pregnancy successfully treated by adrenocortical hormones is discussed.

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PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

Report of Three Cases, Two with Survival of Five Years

BY

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SINCE the publication of the early case reports of primary carcinoma of the Fallopian tubes numerous other reports have appeared in the world literature in a steadily increasing stream, particularly during the past decade. This appears to be partly due to better diagnosis and partly due to more frequent reporting, leading one to think with Latchner (1957) and many others that the condition is more frequent than is generally believed. Comparatively few 5-year survivals have been reported, perhaps under 5 per cent, and about a quarter of all cases recur within a year, although Novak (1957) suggests that previous pelvic inflammatory disease may improve the prognosis by restricting spread through the fimbrial end of the tube. A review of the papers published in the English-speaking countries reveals a number of points which if more widely recognized might lead to better results.

In the first place the symptomatology is varied and at times misleading but probably most cases exhibit a bloody discharge associated with the finding of an adnexal mass. A bright yellow discharge is said to be characteristic but the present author has seen such a discharge with an adnexal tumour, which proved to be of a chronic inflammatory nature and into which haemorrhage had taken place. Both history and examination were similar to those in the three cases reported here. Infertility is said to be more common than parity, but was not so in my patients.

The condition is said to be equally common in either tube and bilateral in about one-third. Its association with tuberculosis is thought by many to be fortuitous but Fullerton (1940) states that he has seen several instances of tubal tuberculosis incorrectly diagnosed as carcinoma.

Only a few authors claim to have made a correct pre-operative diagnosis but an incorrect diagnosis does not matter provided that operation is not delayed and that a correct diagnosis is made at the time of surgery. Unfortunately case reports suggest that pre-operatively the condition has often been mistaken for the pelvic inflammatory disease with which it may well be associated and more surprisingly that the diagnosis is not considered at the time of operation. This is well illustrated by the 10 cases reported by Frankel (1956); only one case was correctly diagnosed at operation and as a result incomplete surgery was performed in 50 per cent. It is hoped that the photographs published with this paper will help to show the probable appearances at operation.

Several authors have suggested means by which a more accurate diagnosis could be made. Vaginal smears may be helpful, but Israel, Crisp and Adrian (1954) report a case in which this was negative. Martzloff (1940) advocates hysterosalpingography but most will agree with Emge (1948) that this is neither safe nor practical. Rhu (1957) sensibly suggests opening all tubal masses at operation and employing frozen sections but such facilities will not be available to all.

Perhaps the best pointer to improved diagnosis is the finding by Willis (1948) that metastases in the iliac and para-aortic lymph nodes are commonly present at autopsy. Possibly dissemination to the para-aortic nodes occurs

early and directly. Removal of any enlarged nodes is essential and perhaps the iliac nodes should always be removed and the para-aortic nodes carefully inspected. Operation should be as radical as can be performed with safety. Most cases have received post-operative deep X-ray therapy with doubtful benefit. In retrospect my first case would probably not have survived without it, but in the second case it would have been wiser to refrain from giving it.

Hu, Taymor and Hertig (1950) found a fairly consistent correlation between histological grading and survival although others have not found this to be so. In their series the surgery has been more complete than in most others reported and perhaps if the surgery is adequate the prognosis does then depend more upon the nature of the growth. Of my three cases the first would fall between their grades II and III, papillary alveolar, and the second and third between their grades I and II, papillary, but with the invasion of the tubal wall in the second case.

Case Histories

Case 1

Mrs. E.B., aged 48 years, para-1. This patient was first seen on 28th November, 1952 complaining of an intermenstrual brown discharge present for three months. Menstruation had been regular and unaltered. During the week preceding admission to hospital the discharge became bright yellow. There was also a complaint that a small swelling in the left groin had been present for the same length of time.

Examination revealed a thin, fairly fit woman with some anaemia. A right adnexal swelling about 6 cm. in diameter was present, being adherent to the uterus and pelvic wall. A small left femoral hernia was also found.

The provisional diagnosis was carcinoma corporis uteri with secondary growth in the right ovary. Operation was undertaken on 9th December, 1952 and the operative findings are well shown in the photograph (Fig. 1). Total hysterectomy and bilateral salpingo-oöphorectomy were performed with removal of the pelvic peritoneum, to which the mass was adherent, as far as the pelvic brim on the right side. The iliac nodes were not enlarged but an isolated enlarged para-aortic node was present and was excised. Femoral herniotomy was carried out.

A blood transfusion was given during the operation and subsequent convalescence was uneventful. Post-operative radiotherapy was arranged at Mount Vernon Hospital, 26 treatments being given between 8th January and 12th February, 1953. The minimum dose to the primary area was 4387·5 r.

This patient has remained fit and well and was without evidence of recurrence up to the present time.

Pathology. Section shows a Fallopian tube containing a carcinomatous mass which is widely infiltrating the muscle coat but which does not quite penetrate it. The tumour has a somewhat variable appearance. Large areas are entirely anaplastic but in some parts its structure is that of a poorly differentiated adeno-carcinoma. These glands show well-marked metachromasia indicating mucus-secreting activity.

Section of the para-aortic node shows it to be almost entirely replaced by a papillary carcinoma in which a few mucus-secreting cells are present. There are occasional mitotic figures.

Case 2

Mrs. L.R., aged 68 years, para-10, was first seen in December, 1952 with a history of two-weeks vaginal bleeding preceded by a yellow discharge for one week. The patient had discarded a surgical corset because pressure of the corset in the left iliac fossa caused pain followed by vaginal bleeding. Because of prolapse a ring pessary had been worn for five years and had been removed after the bleeding had commenced. There was mild hypertension and marked obesity.

Examination under anaesthesia on 9th January, 1953, revealed vaginal and vault prolapse; a fixed mass 6 to 8 cm. in diameter was present in the left adnexal region. Dilatation of the cervix released watery, bloodstained fluid, and curettage produced no endometrium. In the light of the previous case a correct pre-operative diagnosis was made.

Operation was undertaken on 13th January, 1953, the findings at operation being shown in the photograph (Fig. 2). The tumour was adherent to the pelvic colon and to the pelvic peritoneum overlying the left ureter. A careful search revealed no enlarged lymph nodes. After mobilization of the tumour total hysterectomy and bilateral salpingo-oöphorectomy were performed. Convalescence was entirely uneventful. Radiotherapy was arranged at Mount Vernon Hospital, 26 treatments being given between 5th February and 12th March, 1953. The minimum dose to the primary area was 4052·5 r.

Pathology. The wall of the Fallopian tube is hypertrophied; the lumen is distended by a fairly well differentiated adenocarcinoma which is infiltrating the muscularis in places. Considerable fresh haemorrhage is present in the growth and there is evidence of old haemorrhage at the periphery of the Fallopian tube.

FIG. 1
Operation specimen—Case 1.

FIG. 2
Operation specimen—Case 2.

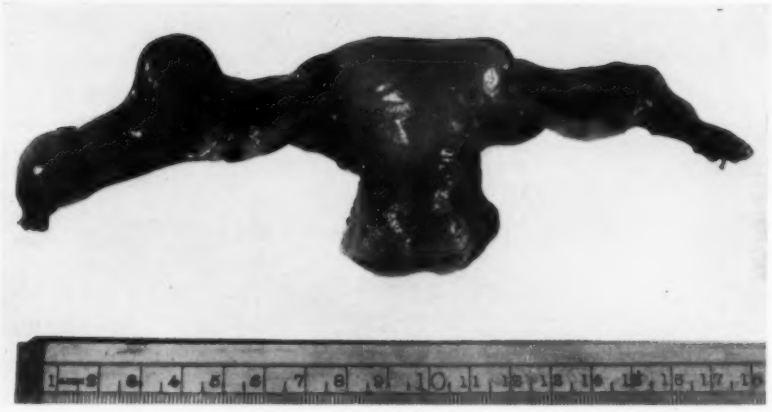

FIG. 3
Operation specimen—Case 3.

Follow-up. Unfortunately severe mental and physical reactions followed the radiotherapy but mental recovery was complete within a few months although physical recovery was much slower and never complete. Progress was maintained for the first year but then severe backache developed followed by root pains and difficulty in ambulation. X-rays in April, 1954 demonstrated collapse of L5 vertebra, thought at that time to be due to a metastasis. Deep X-ray therapy was given but was without real effect. Ambulation was further impaired by a subcapital fracture of the left femoral neck which occurred later in the same year without any history of trauma.

Since 1954 the patient's condition has remained relatively unchanged. There is induration in the lower abdomen, but no other evidence of local recurrence. Further X-rays were taken in December, 1957 and compared with previous films. These films show osteoporosis of the dorsal and lumbar spine; the inferior plate of L2 is concave and in L5 there is marked concavity of both plates with some loss of vertebral height. These appearances suggest compression fractures in osteoporosis and are not characteristic of metastases.

This old lady, now 73, gets about quite well in a wheelchair and even manages a little gardening.

Case 3

Mrs. G.G., aged 60 years, para-1, was first seen on 29th April, 1958 because of slight post-menopausal bleeding for the preceding three weeks. There had been one pregnancy ending in a difficult confinement; a late menopause occurred at the age of 55 years.

Examination under anaesthesia on 6th May, 1958 revealed no abnormality other than a scanty blood-stained discharge but dilatation of the cervix produced a quantity of heavily blood stained watery fluid. Curettage produced no material for examination.

Although no adnexal tumour was palpable, a tubal condition was considered possible and a laparotomy was undertaken on 19th May, 1958. An early carcinoma was present in the distal portion of the left Fallopian tube. Proximally there was a small haematosalpinx. The fimbrial end of the tube was normal in appearance. No enlarged lymph nodes were present but unfortunately there were a number of small nodules 1–2 mm. in diameter on the peritoneum between the infundibulo-pelvic ligament and the pelvic colon.

Total hysterectomy and bilateral salpingo-oöphorectomy were performed. The external iliac glands on the left side and the area of peritoneum referred to above were removed as completely as possible (Fig. 3).

Pathology. Section shows a papillary carcinoma of the Fallopian tube. There is an extensive, delicate, supporting stroma of cellular fibrous tissue covered by many layers of neoplastic cells which are frequently vacuolated but which are rarely in mitosis. The muscular wall of the tube is stretched out thinly over the growth but is not infiltrated by it.

The peritoneal nodules show secondary carcinoma in a much more active state than the primary tumour. There are many mitoses.

The lymph glands show no evidence of invasion.

The post-operative period has been uneventful and a course of super-voltage X-rays has been arranged.

Summary

Three cases of primary carcinoma of the Fallopian tube are reported, two of the patients having survived for more than five years after operation. It is suggested that the most important factor in prognosis is correct diagnosis on the operating table enabling the necessary radical procedure to be carried out. Attention is called to the likelihood of early metastasis to the para-aortic lymph nodes. The third case illustrates the possible effect on prognosis of previous pelvic inflammatory disease. Although the condition was in an early stage, malignant cells had established themselves in the pelvic peritoneum close to the fimbrial end of the tube. Had this been closed by previous inflammation such early extension would probably not have occurred.

Finally it is clearly better to perform a laparotomy in a case of pelvic inflammatory disease than to risk the possibility of treating a carcinoma conservatively.

Acknowledgments

I should like to record my thanks to my colleagues in the Radiotherapy Departments of the Middlesex Hospital and the Mount Vernon Hospital, to Dr. Eric Topham for reviewing the X-ray films, to Dr. N. D. Gower for the histological reports, and to Miss W. Shaw for her photography.

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THE HOUR OF DELIVERY

BY

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THE impression is prevalent among obstetricians and midwives that proportionately more deliveries occur during the night hours than during the day hours. Some years ago a question regarding this difference was answered in the negative by the *British Medical Journal* (1952). But then Simpson (1952) presented a summary of 4,031 births in the Lancashire County Council's Health Division No. 17, showing that 55·5 per cent of these births occurred during the hours between 11 p.m. and 11 a.m., as against 44·5 per cent between 11 a.m. and 11 p.m. A detailed analysis of over 16,000 deliveries was published by Charles (1953), who found also that "55·6 per cent of all deliveries occurred in the 12-hour period 9 p.m. to 9 a.m., the peak delivery time being about 3 a.m." Charles analyzed his figures also specifically, by parity and place of birth (domiciliary and institutional), as well as compared the time of onset of birth with the time of delivery. Bradford Hill (1955) in his *Principles of Medical Statistics* quotes statistics from New York State 1915–25, according to which 54·0 per cent of live births but only 47·0 per cent of stillbirths occurred in the time period from 9 p.m. to 9 a.m. Whereas there is a striking conformity in figures of live births, in stillbirths Charles found also a preponderance in night hours. It seems anyhow from these papers that a difference in incidence of births in day and night cannot be denied.

This fact is important not only from an administrative point of view. Understanding the reasons underlying the difference may provide a clue to a deeper understanding of the process of delivery.

In the present paper an analysis is presented of 20,500 normal deliveries of Jewish women in Israel, during the period 1940–50. Thanks to the very heterogeneous composition of Israel's population, particularly during and after the unprecedented immigration of 1948–51, this material gives special possibilities of differential analysis and comparisons. The characteristics of the population and its breakdown were described by the authors in a previous paper and may be consulted there (Halevi, Bromberg and Brzezinsky, 1951).

The material was collected in several hospitals in Israel and covers a wide differential of the Jewish population during the Mandatory period and in the State of Israel. Only the hour of delivery was notified, because there is no exact registration of the hour of onset of birth. In the following tables we used a 24-hour designation of time and designated each hour by the starting hour, i.e., deliveries occurring at hour 14— means all deliveries which occurred between 2 and 3 p.m. Whereas over 90 per cent of Jewish deliveries in Israel are institutional we could not compare these deliveries with domiciliary, and our material is actually representative of all Jewish deliveries in Israel.

The frequency distribution of all deliveries by hour is shown in Table I.

52·14 per cent of all deliveries occurred between 6 p.m. and 6 a.m. This is a smaller proportion than found in the English and American surveys. The concentration of deliveries in certain hours becomes more evident by breaking down the 24-hours circle into 8 three-hour periods. (Table II.)

From 11 p.m. to 5 a.m. is the peak period

TABLE I

Frequency Distribution of All Births by Hour of Delivery

Hour	No.	Per Cent		
24–1	866	4·23		
1–2	984	4·80		
2–3	987	4·81		
3–4	878	4·29	26·47	
4–5	867	4·22		
5–6	845	4·12		
6–7	843	4·12		
7–8	863	4·20		
8–9	878	4·28		
9–10	853	4·16	24·83	
10–11	817	3·98		
11–12	838	4·09		
12–13	761	3·71		
13–14	776	3·78		
14–15	770	3·75		
15–16	783	3·84	23·03	
16–17	796	3·89		
17–18	833	4·06		
18–19	876	4·29		
19–20	801	3·91		
20–21	838	4·08		
21–22	848	4·14	25·67	
22–23	902	4·40		
23–24	997	4·85		
Total ..	20,500	100·00		

of deliveries, taking 27·20 per cent of the total; while from 11 a.m. to 5 p.m. is the ebb, when only 23·06 per cent of deliveries take place.

We proceeded then to examine the concentration of deliveries by various differentials. Deliveries of females are more concentrated than those of males. During the 8 hours from 8 p.m. to 4 a.m. 35·06 per cent of male deliveries and 36·19 per cent of females occurred. This difference is statistically not significant (only 1·7 times the Standard Error).

The age distribution of the delivered women could have some influence on our problem. If the hour of delivery is influenced by some psychological fear then the accumulation during night will be more pronounced in young mothers and in low parity.

TABLE II

Concentration of Deliveries in Three-Hour Periods

Hours	Per cent of All Deliveries		Index Number (Mean=100)	
17–19	12·26	24·88	98·0	99·5
20–22	12·62		101·0	
23–1	13·88	27·20	111·1	108·9
2–4	13·32		106·7	
5–7	12·44	24·86	99·6	99·5
8–10	12·42		99·5	
11–13	11·58	23·06	92·7	92·2
14–16	11·48		91·7	
	100·00			

TABLE III

Percentage of Deliveries at Certain Periods at Night, by Age of Woman

Hours	Age of Woman					
	15–19	20–24	25–29	30–34	35–39	40–44
8 p.m.–8 a.m.	50·7	52·8	51·8	53·4	51·0	50·6
8 p.m.–4 a.m.	34·6	35·8	35·1	36·4	34·8	37·9
	Index Numbers*					
8 p.m.–8 a.m.	101·4	105·6	103·6	106·8	102·0	101·2
8 p.m.–4 a.m.	103·9	107·5	105·4	109·3	104·5	113·8

* Percentage of actual to expected deliveries.

In all groups there is a greater accumulation of deliveries in night hours, particularly between 8 p.m. and 4 a.m. There is no obvious trend by age of the mother and it seems not to exert any influence on the hour of delivery.

The analysis by parity shows a more resolute and pronounced trend.

TABLE IV

Percentage of Deliveries at Certain Periods at Night, by Parity

Hours	Parity			
	I	II–III	IV–VI	VII+
8 p.m.–8 a.m. ..	50·2	52·5	54·9	54·0
8 p.m.–4 a.m. ..	34·5	35·7	37·9	37·3
	Index Numbers*			
8 p.m.–8 a.m. ..	100·4	105·0	109·8	108·0
8 p.m.–4 a.m. ..	103·6	107·2	113·8	112·0

* Percentage of actual to expected deliveries.

The accumulation in night hours of deliveries of multigravidae is very clear. This is in accordance with the findings of Charles who noted that "delivery times for primigravidae show less diurnal variation than do multigravidae, and are, in fact, approximately evenly distributed throughout the 24 hours". Even among the multigravidae there is a clearly pronounced trend to increase with advancing parity. The differences in percentages of the different parities are statistically significant.

An important differential is the community of the mother. The community is to be considered an indication of culture, education and economic level. The Ashkenazim (European Jews) are the most educated and cultural part of the population being also on the relatively highest economic level. Next to them come the Sephardim ("Spanish" Jews) and then the Orientals. The Yemenites are similar to the Sephardim and Orientals in their actual status, although they are known for their inborn intelligence. (Table V.)

The night accumulation is greater for Sephardim and Orientals than for Ashkenazim. These differences are not statistically significant, except that between Ashkenazim and Sephardim in the 12-hour period, where it is just twice the S.E. The Yemenites show an extraordinary picture. Their concentration in the 12-hour period is equal to the Ashkenazim, while in the 8-hour period their actual percentage is less than the expected one. That means that their concentration is to be attributed to the period 4 a.m.–8 a.m. We cannot see any acceptable explanation for it.

No difference was found between the concentration in institutions serving urban or rural populations, new immigrants or veteran inhabitants of the country. Only one hospital, serving almost an exclusively urban population forms an exception to the rule, having 38·7 per cent of its deliveries between 8 a.m. and 4 p.m. On the other side the night predominance is evident in all other hospitals in this town too. (Table VI.)

It is very difficult to trace in these figures any influence of the economic status or locality, and apparently they are of no validity for our problem.

If the concentration of deliveries during the night is connected with sunlight, we should find a difference by seasons. But the fact that this concentration is noticeable mainly late in

TABLE V

Percentage of Deliveries at Certain Periods at Night, by Community of Women

Hours	Ashkenazim	Sephardim	Orientals	Yemenites
8 p.m.–8 a.m.	52·1	53·9	53·4	52·3
8 p.m.–4 a.m.	35·7	36·0	36·9	32·8
		Index Numbers*		
8 p.m.–8 a.m.	104·2	107·8	106·8	104·6
8 p.m.–4 a.m.	107·2	108·1	110·8	98·6

* Percentage of actual to expected deliveries.

TABLE VI

Percentage of Deliveries at Night Periods at Certain Hospitals

Hospital	Population Served	Percentage of Deliveries Between	
		8 p.m.–8 a.m.	8 p.m.–4 a.m.
Hadassah, Tel Aviv	Urban, middle class	46·5	33·0
Assutah, Tel Aviv	Urban, higher economic level ..	51·6	34·1
Zahalon, Jaffa	Urban, new immigrants	51·3	36·1
Assaf Harofeh, Zerifim	Rural, new immigrants	53·0	34·1
Hadassah, Jerusalem	Urban, predominantly veteran ..	53·5	36·6
Central, Affulah	Rural, veteran	51·4	34·9

the evening and early in the morning makes such an examination difficult. The period when the light is changing in Israel between summer and winter is 4 to 8 a.m. and 4 to 8 p.m. An analysis of our figures showed the following percentages of deliveries in these periods.

TABLE VII
Percentage of Deliveries at Certain Periods of Day and Night by Seasons

Season	4–8 a.m.	4–8 p.m.
November–February ..	16·9	16·0
March–June	16·4	16·0
July–October	16·7	16·3

The highest proportion of deliveries during 4 to 8 a.m. was in February and September, while the lowest proportions were in August and December. During 4 to 8 p.m. the highest proportion was found in December and the lowest in March. It seems that seasonal changes in light do not influence the accumulation of deliveries at certain hours.

Finally any possible connexion between accumulation of deliveries in the night and the weight of the newborn was examined. (Table VIII.)

Because of the small number of observations we may disregard the first column of very small prematures. In the other weight groups a trend seems to be evident that the concentration gets smaller with the increase in weight of the newborn. This is more evident when the 8-hours period is taken.

SUMMARY

(1) Twenty thousand five hundred Jewish births in Israel are reviewed with regard to the hour of delivery. The highest proportion in 3-hour periods was found between 11 p.m. and 2 a.m. (13·9 per cent); in 6-hour periods 27·2 per cent of deliveries occurred between 11 p.m. and 5 a.m., while between 11 a.m. and 5 p.m. 23·1 per cent of deliveries occurred.

(2) Multigravidae have a higher concentration of deliveries in the night hours than primigravidae.

(3) Mothers of Oriental origin have a higher concentration during night hours than European mothers. Yemenites are similar in this respect to Europeans. These differences are statistically insignificant.

(4) Age of mother, season, urban versus rural localities and the length of stay in Israel seem to be of no influence on the hour of delivery.

(5) Prematures seem to be concentrated at night more than mature infants.

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TABLE VIII
Percentage of Deliveries at Certain Periods at Night by Weight of Infant

Hours	Weight of Infants				
	1,000–1,599 gr.	1,600–2,399 gr.	2,400–2,999 gr.	3,000–3,599 gr.	3,600+ gr.
8 p.m.–8 a.m.	51·0	53·4	52·1	52·2	52·5
8 p.m.–4 a.m.	32·3	37·8	36·2	35·5	34·9
No. of deliveries ..	96	671	5,070	10,522	4,119

THE TREATMENT OF TRICHOMONATOUS VAGINITIS WITH TRICHOMYCIN GIVEN ORALLY

BY

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IT is generally agreed that the available treatments of trichomonatous vaginitis are unsatisfactory. Indeed the very large number of local treatments by means of chemicals, hormones and antibiotics which have been reported as useful is itself a testimony to the lack of perfection of any.

After an initial improvement relapse is common usually following the next monthly period. It is considered that vaginal recurrence may result from internal reinfection from residual trichomonads in Skene's tubules and other sites, or from external reinfection from the male consort. The need of a systemic treatment of the disease has long been apparent for such might not only kill trichomonads beyond the reach of vaginal pessaries but could also be used to clear hidden infection in the male partner. Indeed trials have been undertaken with atebrin (Hammer, Degroat and McGregor, 1954), chloroquine (Swartzwelder *et al.*, 1955), aminitrozole (Barnes *et al.*, 1957; Catterall and Nicol, 1957; Willcox, 1957) and with trichomycin (Magara *et al.*, 1954; Catterall and Nicol, 1957).

If initial reports (e.g., Gardner and Dukes, 1956, with amnitrozole) have sometimes suggested promising activity further studies have indicated a complete failure of these substances to control vaginal trichomoniasis. The present report concerns the use of the antibiotic trichomycin.

TRICHOMYCIN

Trichomycin is a Japanese antibiotic made from the soil actinomycete *Streptomyces hachijoensis* which takes its name from the Island of Hachijo from where the soil sample was originally obtained. It was isolated by Hosoya and his colleagues (1950, 1952) at the University of Tokyo.

Trichomycin is a yellow powder claimed as potent upon protozoan parasites, fungi and yeasts. It is used topically in vaginal thrush, trichomonatous vaginitis and fungal skin conditions. It was shown to be effective locally in trichomonatous vaginitis by Magara *et al.* (1954).

The manufacturers claim that if the tablets are inserted high into the vagina trichomonads (and candida) will disappear after 1–3 doses although for the prevention of reinfection and for complete cure 6–10 doses may be preferable.

CASE MATERIAL

Sixteen patients with trichomonatous vaginitis are involved in this study. Their average age was 30·6 years (extremes 18–52), 9 were married and 7 were single. Three were Negresses, one from the West Indies, and the remainder were white-skinned persons, 10 from the United Kingdom, 2 from Greece and 1 from Eire. Only 4 had had no previous venereal incident, the remainder having had 8 previous attacks of gonorrhoea, 11 of vaginitis (*T. vaginalis* having previously been found in 6) and one each of syphilis, pediculosis pubis and vaginal boil. Two persons had been examined as contacts of males with gonorrhoea or non-gonococcal urethritis. The

total of 24 previous incidents represented an average of 1·5 for the group. One patient had had a hysterectomy for fibroids.

Trichomonads were found in all cases by darkfield examinations of wet specimens of vaginal discharge before treatment and similar specimens were examined as soon as possible after completion of therapy. Smears and cultures for gonococci from both urethra and cervix were made on all patients before treatment. Gonococci were found in 6 and parenteral penicillin was given in addition in these cases. The Wassermann and VDRL reactions were negative in 15 cases and in one the Wassermann reaction was weakly positive. The gonococcal complement-fixation test was made from sera from 13 patients, the result being negative in 12 and anti-complementary in one.

Trichomycin Given Orally

Trichomycin was given orally to 13 patients. Eleven patients received 2 tablets of 20,000 units four times a day (a daily dose of 160,000 units) for periods of 3–7 days with a total dosage of 20–54 tablets or 400,000–1,080,000 units. One patient was treated with tablets of 50,000 units (400,000 units daily) to a total of 32 tablets or 1,600,000 units over 4 days. One patient immediately defaulted. All but one of the remainder still had motile trichomonads in the vaginal discharge at the conclusion of treatment. In one patient (given 1,080,000 units over 7 days) they were still present at 3 days but when the patient next returned 20 days from the onset of treatment they could not be found. Thus of the 12 patients given 400,000–1,600,000 units, 11 were followed and there were 10 failures (90·9 per cent). The last patient was given 16 tablets each of 50,000 units (total 800,000 units) to take over 4 days. She lost the tablets before she had taken any of them and when she returned after one week trichomonads could not be found.

The antibiotic was well tolerated and no side-effects were reported. The results are summarized in Table I.

Trichomycin Given Locally

Two of the above failing cases and 3 additional cases of trichomonatous vaginitis were treated with trichomycin vaginal tablets without oral medication. Each tablet contained 50,000 units of trichomycin plus 50,000 units of crystalline penicillin, tartaric acid and soda bicarbonate. The yellowish tablets thus "foamed" in the presence of moisture. As but a few tablets were available it was only possible to use them on these 5 patients once nightly for periods of 2–7 days.

Table I

Trichomycin Given Orally in Trichomonatous Vaginitis

Case No.	Tablets Taken q.d.s.	Dose per Tablet in Units	Daily Dose in Units	No. of Tablets Taken	Days of Treatment	Total Dosage in Units	Result
1	2	20,000	160,000	20	3	400,000	Trichomonatous vaginitis+ at 3 days
2	2	20,000	160,000	24	3	480,000	Trichomonatous vaginitis+ at 3 days
3	2	20,000	160,000	24	3	480,000	Trichomonatous vaginitis+ at 3 days
4	2	20,000	160,000	26	3	520,000	Trichomonatous vaginitis+ at 3 days
5	2	20,000	160,000	28	3½	560,000	Trichomonatous vaginitis+ at 4 days
6	2	20,000	160,000	28	3½	560,000	Trichomonatous vaginitis+ at 7 days
7	2	20,000	160,000	32	4	640,000	Trichomonatous vaginitis+ at 4 days
8	2	20,000	160,000	40	5	800,000	Defaulted
9	2	20,000	160,000	40	5	800,000	Trichomonatous vaginitis+ at 7 days
10	1	50,000	200,000	16	4	800,000	Lost tablets. Trichomonatous vaginitis− at 7 days
11	2	20,000	160,000	54	7	1,080,000	Trichomonatous vaginitis+ at 7 days
12	2	20,000	160,000	54	7	1,080,000	Trichomonatous vaginitis− at 20 days
13	2	50,000	400,000	32	4	1,600,000	Trichomonatous vaginitis+ at 7 days

One patient treated for 2 days still had demonstrable trichomonads at 7 days. They were not found, however, at the end of treatment in one patient treated for 3 days although she complained that the tablets did not dissolve well. Trichomonads were found at the end of treatment in both of 2 patients treated for 4 days. One patient was treated for one week but unfortunately she then defaulted from observation.

Summary and Conclusions

(1) Trichomycin, a Japanese antibiotic reported to be active against *T. vaginalis*, has been used orally in the treatment of 13 cases of trichomonatous vaginitis in a total dosage of 400,000–1,600,000 units given over 3–7 days.

(2) One patient lost her tablets before taking any and another defaulted before the results of therapy could be observed. Of the remaining 11 motile trichomonads were found in the vagina after treatment in 10 (90·9 per cent).

(3) The antibiotic was well tolerated and no side-effects were reported.

(4) The drug was used locally in 5 cases, one tablet being inserted into the vagina each night for periods of 2–7 days. One patient defaulted and trichomonads were demonstrated after treatment in 3 of the 4 remaining cases. The treatment duration was so short, however, that no firm conclusions should be drawn although trichomonads have been claimed to have disappeared following only 1–3 vaginal tablets of trichomycin.

(5) It is concluded that trichomycin in the doses given orally had little or no demonstrable effect upon *T. vaginalis* in the vagina.

Acknowledgments

Grateful acknowledgments are expressed to the Fujisawa Pharmaceutical Co. Ltd., of Osaka, Japan, who kindly provided the trichomycin used in this study.

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DYSTOCIA DUE TO DISTENSION OF THE FOETAL BLADDER

BY

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THIS case is described in view of the great rarity of the congenital abnormality of the foetus which gave rise to dystocia in the second stage of labour.

CASE REPORT

Mrs. A.M., aged 39 years, had a previous obstetric history of 3 normal deliveries and one miscarriage at sixteen weeks. No congenital abnormalities had occurred in the family. Her last normal period had been on 13th October, 1957 and the date of delivery was estimated to be 20th August, 1958.

The blood group was B, Rhesus + and the haemoglobin 13 g. per cent.

Pregnancy proceeded normally apart from a persistent low grade trichomonal infestation which was treated by vaginal swabbing with 1 per cent picric solution and by Locan pessaries. The blood pressure and urine remained normal.

The patient was admitted on 14th August, 1958 to Cresswell Maternity Hospital, Dumfries, on account of slight painless ante-partum haemorrhage of 2-hours duration which had ceased on admission to hospital.

The general condition of the patient was good, the blood pressure being 125/85. The temperature and pulse rate were normal.

The uterus was of normal tone and the foetus presented by the head which was not engaged. The height of the fundus was consistent with the duration of the pregnancy and the foetal heart was regular at 120 beats per minute.

Vaginal examination confirmed the presentation and no placental tissue could be felt near the cervix which was partially taken up and one finger-breadth dilated. The membranes had ruptured spontaneously at some time before admission.

Labour began within a few hours and progressed normally through the first stage and the second stage until the head of the foetus was delivered without any difficulty and then progress ceased. The uterine contractions continued regularly but attempts to deliver the shoulders by traction failed. Vaginal examination beyond the foetal head revealed no cause for the delay. By now the foetal heart could no longer be heard.

Following the induction of general anaesthesia examination *per vaginam* with the whole hand could reach beyond the foetal shoulders and above the maternal pelvic brim when a firm cystic swelling was palpated in the foetal abdomen. No contraction ring was present. As the foetus was dead the swelling was opened into by Simpson's perforator, but not without considerable difficulty due to the awkward access past the foetal trunk to a level above the pelvic brim.

Clear fluid drained freely and by traction on the head the foetus was delivered. The placenta and membranes were expressed and the total blood loss was normal.

The mother's recovery was uneventful.

The child, a stillborn male, weighed 5 pounds (2,267 g.) and was normally developed apart from the urogenital tract.

The bladder was enormously distended and thin-walled, the estimated capacity being 4 pints (2,000 ml.). The right ureter was dilated to the thickness of a pencil and the dilatation continued into the kidney pelvis compressing the kidney tissues. The urethra was obstructed in the posterior portion by a fibrous atresia. The left kidney contained multiple small cysts and the ureter consisted of a solid fibrous cord. Both testes were undescended and attached to the back of the bladder.

DISCUSSION

The occurrence of dystocia due to great enlargement of the foetal bladder is very rare and in a review of the literature only 8 cases of this type were found. In 2 of these, reported by Jeffcoate (1931) and by Still (1955), there was no evidence of obstruction of the urinary tract and in the remainder reported by Edgecombe (1930), Savage (1935) and Shaw and Marriott (1949) and by Beacham and Beacham (1952), obstruction was present in some part of the urethra. The majority of the affected children were male. The estimated amount of urine in the bladder varied between 800 and 4,000 ml. In

the case reported by Beacham the external genitalia were absent and the sex of the child was decided by the presence of undescended testicles adherent to the back of the distended bladder, similar to the position in which they were discovered in this case.

The presence of the normal amount of liquor amnii supports the conclusion of Shaw and Marriott that the bulk of the fluid is secreted by the amnion. In the case under review the foetal kidneys were grossly distorted and destroyed by cysts and hydronephrosis so that the renal excretion must have been much less than that of a normal foetus.

The obstruction to the labour did not occur at the pelvic brim but much higher in the maternal abdomen where the enlarged foetal bladder was held in the upper segment of the uterus. Therefore perforation of the swelling was difficult due partly to the presence of the foetal thorax in the maternal pelvis and partly to the distance of the swelling from the vaginal introitus.

Summary

A rare case of dystocia due to distension of the foetal bladder is reported and some observations made on the site of obstruction to labour, and the amount of liquor amnii which was present.

Acknowledgment

I wish to thank Dr. J. Bruce Dewar for his permission to publish this case.

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A NAEGELE PELVIS

BY

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THE subject of this memorandum was a married woman, Dorothy B., aged 25, who presented herself for booking in her first pregnancy in 1955. Term was at the end of January, 1956. There was nothing unusual in her history or physical signs until failure of engagement of the foetal head led me to examine her pelvis in some detail at the 34th week. The lumbo-sacral promontory could not be reached but the pelvis was felt to be contracted transversely. Radiographs disclosed absence of the left ala of the sacrum with oblique distortion of the pelvis typical of the pelvis first described by Naegele except that there is a joint space on the affected side. But her pelvis showed more than this. In the lateral view the body of the first sacral vertebra was small, deformed and round, not cylindrical. Below it was an indeterminate mass of bone representing the rest of the sacrum. There was no coccyx. These two pieces of bone that represented the sacrum and coccyx were directed horizontally backwards and reference to the patient showed what should have been noticed before—a bony projection between the upper part of the buttocks. Superficial examination of the woman had not suggested any deformity until the X-ray pictures were taken.

There was a quite symptomless heart murmur confined to the region of the second left costal cartilage and my physician colleague, after investigation, decided that almost certainly there was an unimportant atrial septal defect. Intravenous pyelography performed later disclosed yet another symptomless congenital abnormality. The right kidney was low in position so that the centre of its pelvis was level with the iliac crest. There was some dilatation of the pelvis of this kidney. The left kidney shadow was normal in position and outline.

Caesarean section was performed on 21st January, 1956, and a healthy boy weighing 6 pounds 11 ounces was delivered. On 6th May, 1957, her second child, a girl weighing 6 pounds 9 ounces, was delivered by Caesarean section and on 16th September, 1958, Caesarean section and tubal ligation were carried out for her third child, a boy weighing 7 pounds 6 ounces. The babies appeared normal and are well.

Franz Karl Naegele was professor of midwifery at Heidelberg and published his monograph in 1839. Until then deformity of the pelvis in the absence of local disease had been attributed only to rickets or osteomalacia. He himself met only one patient with the deformity. She was a primigravida, 19 years of age, whom he attended in 1828. Her brother had been rejected for military service because one hip was higher than the other. The membranes were ruptured for two days before pains began and three days later Naegele applied forceps. Although he could not reach the promontory he found great difficulty, and soon he was wishing he had practised perforation. At last he extracted a dead child. The patient died of puerperal fever on the fifth day and Naegele secured her pelvis. When he had had the pelvis macerated and cleared of its soft parts its appearance immediately brought to his mind two specimens he had seen in the collection of a friend. The only history with one of these two was that she was a primipara and died within twenty-four hours of delivery. The other was

FIG. 1
Antero-posterior view. There is the typical distortion but a joint space is present on the affected side.

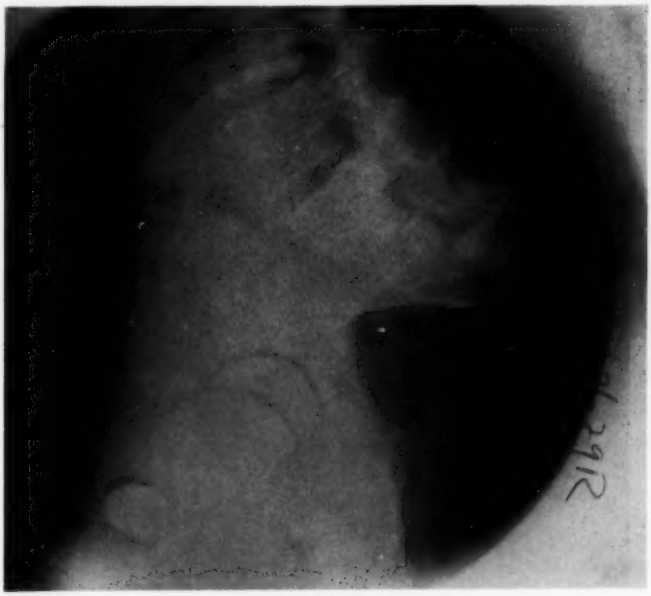

FIG. 2
Lateral view. The lowermost well-formed vertebral body is that of the fifth lumbar. (The heads of the femora and the symphysis pubis have been outlined.)

the counterpart of his own—primipara, 19 years of age, numerous applications of the forceps, stillbirth and death on the fourth day. From friends, former pupils and from his son, Naegele began collecting details of pelves and in some cases the bones themselves, from all over Europe. When he published his monograph in 1839 he described 37 cases (including two of the condition in men) from Paris, Vienna, Bremen, Milan, Amsterdam, Basle, etc. Professor Montgomery of the Medical School, Park Street, Dublin, sent him a drawing of one in his collection and Hermann Franz Naegele, the son of Franz Karl, went over to Dublin to measure the pelvis. Many of these pelves had no history attached to them and indeed some were rescued from the charnel houses of those who prepared bones for anatomists and one was the pelvis of an Egyptian mummy. In 11 cases a history was available. Ten of them were primigravidae and all of them died either undelivered or soon after delivery of injury or sepsis. All the babies were dead. The eleventh was notable. She had 6 children all normally delivered except the fifth which was extracted by forceps. Three weeks after a quick normal delivery of her sixth child she died of peritonitis. The pelvis was sent from Berlin for Naegele to examine.

Naegele's monograph is remarkable for its meticulous exactitude and in it he laid down six features of the deformity he was the first to describe:

(1) Complete fusion of one sacro-iliac joint.

(2) Absence of development or imperfect development of one half of the sacrum with narrowing of the anterior sacral foramina on the side corresponding to the ankylosis.

(3) On the same side diminished breadth of the hip bone and its sciatic notch.

(4) The sacrum seems pushed to the ankylosed side with its anterior surface more or less turned towards that side. At the same time the pubic symphysis is displaced to the opposite side.

(5) On the ankylosed side the lateral wall of the pelvis is flattened compared with a normal pelvis.

(6) On the other side the pelvis is no bigger than in a normal pelvis.

It will be seen from the radiograph accompanying this article that the pelvis now reported fails to fulfil one of these criteria in that there is a joint space on the affected side. Naegele was at pains to make it clear that such cases should be excluded and after giving his classic account he described 4 pelves similar to the subject of his monograph but not true examples of the condition. Three of these 4 pelves had deficient development of half of the sacrum but no ankylosis (details of one of these were sent to him by Edward Rigby from St. Bartholomew's Hospital) and the fourth was a pelvis with one-sided ankylosis but no deficiency of development. This seems an unnecessarily restricted definition of the deformity for the aetiology is the same and, whether a joint space is present or not, the shape of the pelvis and the obstetric problems are identical. Nevertheless if the exact description given by Naegele is adhered to, the pelvis herein described and many of those depicted in text-books, would be excluded.

Naegele was very decided in his view of the aetiology of the condition. He first expounded this in a paper he read on 24th November, 1832, to the Heidelberg Society of Natural History and Medicine. He said "This deformity is not produced by external violence, nor by constitutional disease but is the result of an anomaly of development". In his monograph he re-asserted this opinion and went on to give numerous reasons for it. After Naegele there were many arguments differing from his about the aetiology and, amid the confusion of opinions, the pronouncement of the discoverer of the condition was lost sight of. Even today (Little, 1958) quite different views are erroneously attributed to him. Robert concurred. The presence of what is obviously an additional congenital deformity of the sacrum in the pelvis now described, strongly supports this view.

Without X-rays diagnosis must have been very difficult and in 1839 no case had yet been diagnosed in a living woman. Naegele emphasized that the woman usually had no history of illness, was well built, had a normal external conjugate and on internal examination the promontory was not reached. He went on

to give measurements which should lead to a diagnosis:

(1) From the ischial tuberosity of one side to the posterior superior iliac spine of the other.

(2) From the anterior superior iliac spine of one side to the opposite posterior superior spine.

(3) From the spinous process of the last lumbar vertebra to the anterior superior iliac spine on each side.

(4) From the great trochanter on one side to the posterior superior spine on the other.

(5) From the middle of the inferior border of the symphysis pubis to the posterior superior spine on each side.

Naegele took these measurements on dried pelves. I found them quite useless in the living subject. For the purpose of accurate measurement in a deformed pelvis it is useless to attempt to define the spine of the last lumbar vertebra, the posterior superior spine or even the ischial tuberosity. Contradictory results were obtained in the patient and as a means of making a diagnosis external measurements can be discarded.

On treatment Naegele wrote that unless the pelvis was of large size, Caesarean section was the best treatment and that symphysiotomy was useless for this condition. Indeed since his time little has been added to our knowledge of the aetiology, incidence, description and treatment of the condition and, were it not for X-rays, obstetric tragedies might still occur.

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ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

AT the meeting of Council held in the College House on Saturday, 25th July, 1959 with the President, Professor A. M. Claye, in the Chair, the following Officers were elected or re-elected:

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The following was admitted to the **Fellowship** posthumously:

Horacio José Antonio Conte-Mendoza

The following candidates have been elected to the **Membership:**

Robert Marshall Adam.
Margaret Aureol Austin.
Pamela Mary Bacon.
Gerald Stuart Banwell.
Ajilady Savithri Bhandary.
Debabrata Bhattacharyya.
Sridevi Biswas.
Basil Bloch.
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Aseem Prakash Chakravorty.
Srinivas Krishnama Char.
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Clifton John Ryan.
John Monteith Samson.
Stanley Albert Seligman.
Nigel Gordon Steere.
Doreen Patricia Grieve Stewart.
Roy Harding Syred.
Brenda Anita Taylor.
John Heywood Taylor.
Gytha Wade.
Pearl Allan Walker.
Jayaweera Bandara Wedande.
Charles Richard Whitfield.
Arthur Claude Wilson.

INTERNATIONAL FEDERATION OF GYNAECOLOGY AND OBSTETRICS

THE Third World Congress will take place on 3rd to 9th September, 1961, in Vienna under the Chairmanship of Professor Antoine.

The two main subjects of the Congress will be:

(1) Surgical Treatment in Gynaecology and Obstetrics.
(2) The Role of the Pituitary Gland in the Physiology and Pathology of the Genital organs.

Further information may be obtained from the Secretary General, Dr. H. de Watteville, Maternité, Geneva, Switzerland.

ABSTRACTING OF RUSSIAN LITERATURE

THE Journal is in urgent need of an abstracter of Russian Obstetric and Gynaecological journals for the Review of Current Literature. Will any reader prepared to undertake this service please write to Mr. Stanley G. Clayton, Assistant Editor, 58 Queen Anne Street, W.1.

REPORTS OF SOCIETIES

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

FEBRUARY 1959

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Liverpool on 20th February, 1959. Mr. S. B. Herd took the Chair.

Dr. B. M. Hibbard read a case record of

HYDROPS FOETALIS IN ONE OF UNIOVULAR TWINS

(This article appears on page 649 of this issue)

Discussion

Mr. Herd thought this was the first case of this condition reported to the Society.

Mr. T. F. Redman did not follow the argument about the baby swallowing liquor. According to Bowes, the liquor was changed 8 times in 24 hours which entailed the baby swallowing 16 pints a day.

Mr. J. S. Scott pointed out that if foetal deglutition is absent after the 30th week hydramnios results. Acardiac and acephalic monsters may show hydrops due to failing circulation, and anencephaly is said to be common in cases of uniovular twins.

Dr. S. Bender had seen uniovular twins, one showed hydrops with a hydropic placenta, and the other baby and placenta were normal. Usually hydramnios is confined to one amniotic sac and abates if the foetus dies. He thought that the work on the replenishment of liquor was in doubt.

Professor T. N. A. Jeffcoate pointed out that the rate of turnover of liquor was based on 5 isotope cases only in which there had been a very wide range in results. The liquor reaches the sac by two ways and the renal contribution is significant. Foetal deglutition is an important way in which liquor leaves the sac. Hydramnios does not occur in cases of oesophageal atresia if the atresia is of a certain type—a communication with the trachea from the upper oesophagus, and another communication leading from the trachea to the lower oesophagus.

Mr. P. Malpas commented on the difficulty in making a newborn baby swallow. Hydramnios was as common in cases of foetal abnormality when the oesophagus was normal, and often occurred with a normal foetus.

Mr. H. Roberts had found it possible to drip 1,200 ml. of fluid into the trachea without respiratory embarrassment.

Mr. H. V. Corbett reviewed

ANAESTHESIA FOR CAESAREAN SECTION

The review concentrated mainly on the development of a balanced anaesthetic that has proved most effective in Liverpool. An anaesthetic for Caesarean section should be safe for the mother, avoid anoxia and regurgitation of vomit, and it must give freedom from pain and avoid foetal asphyxia. In the recumbent position the enlarged uterus splints the diaphragm and the effect is increased in both the Trendelenburg and lithotomy positions. Chloroform, and to a lesser extent, ether produce a histo-toxic anoxia, and the same effect is produced by cyclopropane as it is a respiratory depressant. Cardiac arrhythmias may result from cyclopropane and other anaesthetic agents. Muscle relaxants achieve rapid respiratory paralysis and necessitate assisted respiration, and the advisability of intubation in these cases has not been sufficiently stressed. Other causes of anoxia such as ante-partum haemorrhage should be corrected by transfusion. Another major difficulty may arise from vomiting or regurgitation of stomach contents, muscle relaxants increasing this risk. Intubation, therefore, should be performed as early as possible. The use of ergometrine has largely counteracted the relaxant effect of chloroform and ether on the uterus, and it should be more widely recognized that cyclopropane given to patients who recently have had pitocin, increases the tendency to cardiac irregularities and arrest.

It has long been realized that anaesthetic gasses cross the placenta, and this rule must apply to intravenous agents. At first it was thought that the placenta offered a barrier to pentothal for some 12 minutes, and there was, therefore, a need to deliver the child quickly. In 1947 it was established that curare did not cross the placenta, and from this finding the following routine was developed: intubation facilitated by Scoline, followed by a small dose of Pentothal, and the maintenance of light sleep with gas and oxygen.

It now has been shown that Pentothal crosses the placenta within 45 seconds, and thereafter the foetal level approximates that in the maternal blood. These findings suggest that the induction delivery interval was not significant. In the past local analgesia has gained renown in reducing the stillbirth rate, but the method outlined above cannot be incriminated in causing stillbirths. Pethidine may cause foetal depression, and Fluothane has proved dangerously relaxant producing a high incidence of post-partum haemorrhage. Spinal analgesia, though providing ideal operating conditions, has shown too many dangers for its continued use.

Discussion

Mr. Herd commented on the tendency of surgeons to demand ideal conditions, and where these could not be attained local analgesia was desirable. Continued practice for this was essential. He thought the amount of Pentothal was more important than the speed of

delivery. In cases where the shoulders were held by a contraction ring deep flooding with ether might effect delivery.

Dr. D. Menzies preferred to use the term xylocaine or procaine analgesia. There were a few cases where this method should be used. In 300 sections at the Liverpool Maternity Hospital there were 71 cases of procaine analgesia with intravenous pethidine, and in another 4 general anaesthesia was added later. The corrected foetal mortality was 1·3 per cent as against 3 per cent for all cases, and maternal morbidity was 8 per cent.

Dr. K. V. Bailey thought local anaesthesia should not be discarded, but an absolute drill was needed in ward and theatre. Last year he had used the method twice for patients who would not stand general anaesthesia.

Mr. C. J. Dewhurst commented on the different conditions that were required for different cases. When the head was deep in the pelvis uterine relaxation was needed to allow delivery.

Dr. K. V. Bailey presented a paper on

OVARIAN CHANGES CONCERNED WITH GONADOTROPHIC DYSFUNCTION AND ASSOCIATED WITH AMENORRHOEA AND INFERTILITY

(This article appears on page 556 of this issue)

SECOND VENEZUELAN CONGRESS OF OBSTETRICS AND GYNAECOLOGY

THIS Congress will be held in Caracas on 19th to 24th February, 1960.

Further information may be obtained from Dr. H. Marcano Guzmán, Secretary, Apertade 7332 (San Martin), Caracas, Venezuela.

BOOK REVIEWS

"Clinical Obstetrics and Gynecology." Quarterly Book Series. Vol. I, Nos. 1 and 3. Pp. 288 and 303. Illustrated. Paul B. Hoeber Inc., New York, 1958. Four volumes per year—by subscription. Price $18.

JOINT review of the first and third numbers of this interesting new quarterly symposium series seems warranted because all the subjects discussed are essentially "medical" in the broadest sense of this word.

The honour of acting as guest editors for the original number fell to Curtis J. Lund and Allan C. Barnes who respectively were responsible for the subjects of "Medical Problems in Pregnancy" and "Management of Endocrine Problems". In the first section anaemia takes pride of place with full justice done to iron deficiency and megaloblastic types as well as the rarer forms. Sound physiological principles govern the management of heart disease, while team work rather than complex hormone schemes guides the diabetic. Recent fundamental concepts of adrenal and thyroid dysfunction are well documented. Increasing use of intravenous therapy makes the subject of virus hepatitis of considerable significance, but none is more topical than the obstetric management of poliomyelitis patients. In an excellent chapter on urinary infection the management of the occasional problematic drug-resistant case is kept very much in mind.

The endocrine problems discussed by Dr. Barnes and his colleagues are threefold and refer to: (1) Menstrual function; (2) Pregnancy and the puerperium; (3) Growth and sex development. While the aim is to focus attention on management, lack of fundamental knowledge on many aspects necessitates initial concentration on diagnosis and diagnostic methods before a useful discussion of empirical and usually reliable forms of therapy. Chapters on dysfunctional uterine bleeding, dysmenorrhoea, the menopause, adrenogenital syndrome, and precocious sex development are abreast of modern knowledge while those on the endocrine aspects of sterility and threatened and habitual abortion seem to be a little outdated.

"Special Diagnostic Aids" and "Abnormal Uterine Bleeding" are section titles of the third number edited by Paul C. Hodgkinson and John I. Brewer. Diagnostic methods discussed range over a wide field. Vaginal and peritoneal cytological methods are described and evaluated. Culdoscopy and gynography are yet to be evaluated on an extensive scale in this country. No new facts are offered in the chapters on hysterosalpingography, pelvimetry, placentography, blood groups and hypofibrinogenaemia, but chromosome sex determination and cervical mucus crystallization phenomena will be of some interest. Only the editor's own technique and opinions are presented on the controversial subject of cystography.

An exhaustive list of laboratory tests is included in an interesting and searching chapter on diagnosis and treatment of pregnancy toxaemia. The author's revealing and well-founded conclusion that no test alters or indeed helps in the clinical management of cases will come as a blow to the keen investigator.

In the section on abnormal uterine bleeding, the emphasis is on clinical management after thorough investigation and accurate diagnosis. In most instances it seems that function disturbances, regardless of origin, require careful curettage with expert histological interpretation in conjunction with a full and accurate clinical history. Only the simplest regime is prescribed whenever hormone therapy is recommended.

If this review seems a catalogue of contents it is intentional for there is little to criticize. Indeed there is much to praise, especially the uniformly high level of scholarship attained in spite of multiple authorship.

"Proceedings of the Second World Congress on Fertility and Sterility." Edited by PROF. G. TESAURO, Institute of Clinical Obstetrics and Gynecology, Univ. of Naples. Two vols. Pp. 2,948, with 816 illustrations. 1958.

THESE two large and very weighty volumes, whose publication was subsidized by the Italian Government, contain the papers presented and the conferences held at the congress in Naples in May 1956. Workers from 65 nations participated, and the papers are printed with summaries in English, French, German, Italian and Spanish. But each contribution to the round table conferences is printed only in the language used by the speaker so that only a polyglot can obtain full value from these. Four hundred pages are devoted to problems in animal reproduction, and 150 to descriptions of motion-pictures and scientific exhibits shown at the congress.

The critical reader will appreciate that despite great advances in knowledge empiricism has not yet departed from the treatment of infertility. In fact, cheek by jowl are papers lauding and discounting a particular method of investigation or treatment. As an example of the diversity of opinion and experience may be quoted that the methods of detecting ovulation recounted include basal body temperature chart, endometrial biopsy, endometrial cytology, cervical mucus arborization, level of reducing bodies in cervical mucus, vaginal smear, test for occult vaginal bleeding, platelet count and vitamin C elimination test. The sections on the surgical treatment of infertility in male and female are particularly likely to interest clinicians.

These volumes represent a mine of information, positive and negative, to the critical reader, who will

find them most useful books of reference if he has a bookshelf strong enough to support them.

"Hypnosis in Modern Medicine." Second edition, edited by J. M. SCHNECK, M.D. Pp. xix+389. Blackwell, Oxford, 1959. Price 66*s*.

THE new edition of this work, two of whose 11 contributors are from this side of the Atlantic, contains a 25-page section on hypnosis in obstetrics and gynaecology. The author of this section, with its more than 90 references, is Dr. W. S. Kroger of Chicago, well known as the senior author of "Psychosomatic Gynecology". The advantages and disadvantages of hypnosis in labour are fairly given. The wide field for hypnosis in gynaecology is detailed, but with the timely warning that "in our present enthusiasm of pinning the psychosomatic label on many conditions, there is always the danger that the pendulum may swing too far away from accurate scientific evaluation".

S. Bender

"Synopsis of Obstetrics and Gynaecology." By ALECK W. BOURNE, F.R.C.S., F.R.C.O.G. 12th edition. Pp. 640, with 168 illustrations. John Wright & Sons, Bristol, 1959. Price 35*s*.

FROM the preface with its forthright defence of the student's right to a synoptic textbook to the concluding new chapter on intersex, this latest edition preserves the virtues of its predecessors in clarity, practical approach and economy of words and shillings. A few statements may be doubted, e.g., that the breech with extended legs is a bad dilator and likely to prolong labour, and some definitions, e.g., of secondary inertia, may be queried, but the text is remarkably free from being dogmatic and a healthy scepticism is properly evident in some contexts. The traditional chapter heading of contracted pelvis might be better designated pelvic architecture and disproportion, for these provide the main content; in this field the value of intranatal radiography merits mention. This new edition, which, unlike some, is truly up-to-date, will have as much appeal as its predecessors over the last 46 years not only to the student for revision but also to the general practitioner for quick reference.

REVIEW OF CURRENT LITERATURE

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PREGNANCY

224. **Ultrastructure of the Glandular Cells of the Human Endometrium.** (Ultrastruttura della cellula ghiandolare dell'endometrio umano.)

By G. LANZAVECCHIA and E. MORANO. *Minerva ginec., Torino*, **10**, 882–884. Nov. 30, 1958. 9 figs. 11 refs.

The endocellular and endonuclear structure of cells of the endometrium in the secretory phase (17th day) are shown as revealed under the electronic microscope at magnifications up to ×60,000. Further studies may be expected to throw much light on the complicated physiology of the endometrium both in regard to menstruation and pregnancy.

W. C. Spackman

225. **The Reproductive Function in Women Over Forty.** (La funzione riproduttiva nella donne oltre il 4° decennio di vita.)

By A. PEREGO. *Ann. Ostet. Ginec.*, **80**, 585. June 1958. 28 refs.

The author reviews some of the extensive literature relating to childbearing in women over 40.

In a series of 7,624 women, 1·2 per cent of all primigravidae were over 40. Abortion is relatively frequent in older primigravidae. Other complications encountered more frequently included cardiovascular disease, toxaemia and fibroids. The risk of premature labour is increased with advancing maternal age. In labour the need for operative intervention is increased.

The risk to both mother and child appears to be increased. In the present series, 3 mothers died out of 54 (5·5 per cent). There is an increased risk of foetal malformation.

Management of these cases may be fraught with difficulty. The author stresses the value of psychoprophylactic preparation for childbirth.

Josephine Barnes

226. **Radiation Reduction in Diagnostic Obstetrical Radiography: The Application of Electronic Photographic Techniques.**

By R. M. LOWMAN, E. DONNELLAN and S. GOLDENTHAL. *Amer. J. Obstet. Gynec.*, **77**, 18–27. Jan. 1959. 1 table. 7 figs. 6 refs.

In addition to recently developed methods of reducing radiation exposure such as high speed screen combinations, increased aluminium filtration, and high kilovoltage, the authors have introduced an electronic printing device whereby deliberately under-exposed pelvimetry and other films can be revised and their details rendered clear. It is estimated that exposure time can thus be reduced by 60 per cent. The disadvantages are the delay necessary in the film processing and the increased cost.

F. J. Browne

227. **Intrauterine Foetal Monopolar Electrocardiography in Pregnancy and Labour.** (L'électrocardiographie foetale monopolaire intra-utérine au cours de la grossesse et du travail.)

By V. Luca and M. Simionescu. *Gynéc. Obstét.*, **57**, 533–540. 1958. 6 figs. 18 refs.

This short but valuable paper describes the technique of taking electrocardiographic readings by the introduction of a thin, intra-uterine, silver electrode either into the amniotic cavity when the membranes are ruptured or between the membranes and the uterus when the membranes are intact. The skin electrode was placed on the lower abdomen. Their readings show that the foetal heart rate does not vary as one had previously thought with contractions. It is merely that the contracting uterus alters the ability of the observer to hear the foetal heart tones and makes it appear that the foetal heart is slowing during a contraction. They have interesting electrocardiographic records to prove their point.

Elliot E. Philipp

228. **A Study in Experimental Eclampsia.** (Contributo allo studio della eclampsia sperimentale, fattori ormonali nel determinismo della gestosi eclamptica.)

By P. Tartaglia. *Minerva ginec., Torino*, **11**, 55–66. Jan. 31, 1959. 1 table. 15 figs. 92 refs.

Endeavour was made to reproduce the eclamptic syndrome in laboratory animals by the injection of certain hormones. Using 27 non-pregnant controls as against 59 animals (rabbits, guinea-pigs, and rats) in various stages of pregnancy, it was sought to produce the characteristic lesions of eclampsia in the liver, kidneys, adrenals, placentae and foetuses as well as eclampsia-like seizures. Heavy doses were used in two phases: the first a sensitizing course and the second a determining injection 24 hours later. The sensitizing hormones used were DOCA from the anterior pituitary, folliculin, and chorionic gonadotrophin given over several days in large dosage, and the determining hormone a single injection of post-pituitary extract. A further group of animals were given a 5-day course of ACTH before the above sensitizing course.

In the result, the pregnant animals sensitized as above almost all developed evidence of eclamptic changes. If they were in the late stages of pregnancy they aborted dead foetuses and usually died in eclamptiform fits. In early stages, whilst degenerative changes in the organs were found similar to those of human eclampsia, such changes and symptoms were much milder. The non-pregnant animals were to all intents and purposes unaffected. An important observation was that after a 5-day preliminary course of ACTH the animals were almost unaffected, although some near term produced premature though living foetuses.

The author concludes that considerable overactivity in production of hormones by the anterior pituitary, adrenal, ovary and chorion during pregnancy predisposes the organism to eclampsia which is finally determined by overaction of the post-pituitary and suprarenal gland.

[It is common experience that the tendency towards PET can often be checked or arrested simply by hospitalization with its routine of rest and sedation, aimed at producing a relaxed condition of diminished tension, without specific medication. Moreover, the impression is gaining ground that the characteristic tissue oedema of PET and eclampsia is not so much due to sodium retention as to over-production of antidiuretic hormone by the post-pituitary which also allows abnormal permeability of the capillaries.]

W. C. Spackman

229. **Toxaemia and Perinatal Mortality.** (L'influenza della tossicosi nel determinismo della mor alita perinatale.)

By C. A. Cappetti. *Minerva ginec., Torino*, **11**, 103–107. Feb. 15, 1959. 13 tables. 7 refs.

An analysis of 10,987 deliveries at Turin revealed 945 cases of toxaemia, a percentage of 8·6. There was no difference in this proportion over the seven consecutive years analyzed. The perinatal mortality for all deliveries was 2·9 per cent (319 cases), and of the toxaemics 12·26 per cent (116 cases). Toxaemia was equally prevalent in primiparae and for subsequent pregnancies. However, infant perinatal mortality was several times higher for toxaemic I- and II-parae but only slighily higher for multiparae in comparison with the general figures for all deliveries, the percentage figures being 14·5, 10·24 and 3·96 as against 3·21, 2·44 and 2·39.

There was a marked incidence of premature delivery, notably in the first half of the ninth month. This can be regarded as a natural defensive mechanism to interrupt a deteriorating symbiosis between mother and foetus. It carried a corresponding higher proportion of sub-standard foetal birth weights. There was no perinatal foetal mortality in toxaemic mothers where birth weight exceeded 3,000 grammes, 86 per cent of those dying weighing under 2,500 grammes. [No mention is made of the number who came into labour spontaneously as against those brought into labour artificially.]

The method of delivery affected mortality. Whilst maternal safety is more secure by vaginal delivery (including forceps delivery, version and breech delivery), the foetus's best chance was by Caesarean section, and if this method is chosen, classical section is preferred as giving less risk to the mother in such cases. Perinatal mortality in toxaemia was much higher for forceps delivery (except at perineal level), version and breech delivery than for spontaneous delivery, Caesarean section and perineal level forceps delivery which all gave far better foetal results.

W. C. Spackman

230. **Fulminating Eclampsia Treated by Hypothermia.**

By J. E. Malcolm, F. L. A. Vernon, A. J. Merrifield and T. R. Beatson. *Lancet*, **1**, 863–864. Apr. 25, 1959. 1 fig. 4 refs.

The authors report a case of fulminating eclampsia in which the fits continued to occur at about hourly intervals after delivery by Caesarean section. Treatment

by intravenous chlorpromazine, promethazine, pethidine and thiopentone having proved ineffective, hypothermia was induced, the patient being cooled to 92° F. The actual cooling was achieved by an intravenous infusion of pethidine 200 mg., chlorpromazine 100 mg. and promethazine 100 mg. in 500 ml. normal saline, the patient being exposed to cold air from an electric fan. A tracheostomy was performed and the patient's electrolyte and fluid balance carefully controlled. No fits occurred after the start of the treatment and the cooling process was stopped after 48 hours. The patient made an uneventful recovery; the tracheostomy wound closed spontaneously after removal of the tracheostomy tube.

J. M. Brudenell

231. **Aldosterone Excretion and Tissue Electrolytes in Normal Pregnancy and Pre-eclampsia.**

By D. KUMAR, L. A. W. FELTHAM and A. G. GORNALL. *Lancet*, **1**, 541–544. Mar. 14, 1959. 3 tables. 1 fig. 29 refs.

Ten patients attending the antenatal clinic at the Toronto General Hospital were studied in an attempt to define a relationship between aldosterone excretion and tissue electrolytes. Seven of the ten were suffering from mild pre-eclampsia and three were normal. Tissue electrolytes were studied in biopsy specimens of the rectus abdominis muscle, and aldosterone excretion was observed over a twelve-day period during which the patients were in hospital on a controlled sodium chloride intake. It was found that aldosterone excretion rises during pregnancy and that this rise is further increased when the salt intake is restricted. Lower values were obtained in the pre-eclamptic than in the normal patients. The values for total muscle sodium, potassium and chloride in pregnancy and pre-eclampsia were not different from those of normal non-pregnant women. The derived values for *intracellular* sodium, however, showed a *de*crease in normal pregnancy and a considerable *in*crease in pre-eclampsia. No definite correlation between low intracellular sodium values and high aldosterone excretion was found.

J. M. Brudenell

232. **The Human Placenta with Especial Reference to Infarction and Toxemia.**

By D. R. SHANKLIN. *Obstet. Gynec.*, **13**, 325–336. Mar. 1959. 9 tables. 10 figs. 11 refs.

A careful study of 767 placentas was made by the author for the incidence and development of various types of infarcts.

The conclusions reached are that pre-eclamptic toxaemia is not associated with an increase in placental infarcts. Marked changes in the chorionic trophoblast, interpreted as indicative of severe senile degeneration of that tissue, were found consistently in cases of toxaemia.

Infarcts of all types, and marantic thrombi, are considered to arise from focal disturbances in the flow of maternal blood through the intervillous space. These changes are not considered to be a necessary part of placental ageing.

Foci of calcification in the villi occurred equally often in toxaemic and non-toxaemic placentas.

A striking degree of senile change in the trophoblast in cases treated by large doses of diethylstilboestrol suggests that oestrogenic substances play a role in the decline of the placenta.

J. G. Dumoulin

233. **The Role of Urinary Infection and Interstitial Nephritis in the Causation of Vascular Renal Syndromes in Pregnancy.** (Role de l'infection urinaire et de la néphrite interstitielle dans la génèse des syndromes vasculo-rénaux de la grossesse.)

By R. MERGER, J. LÉVY and J. BARRAT. *Gynéc. Obstét.*, **57**, 503–532. 1958. 2 tables. 1 fig. 11 refs.

This is a most interesting and provocative paper dealing with 80 cases in which albuminuria occurred either in pregnancy or labour. The point that the authors make is that every case of albuminuria in pregnant women should be investigated thoroughly, and especially from the point of view of counting the white blood cells in urinary centrifuge deposits. They have discovered that surprisingly frequently, even when symptoms have apparently been relieved, urinary infection as diagnosed by a white blood cell deposit persists. They think that if this simple test is carried out more often, many cases of apparent toxaemia of pregnancy or apparent mild cystitis will be found to be due to interstitial nephritis originally due to an infection.

It is important to follow patients up after delivery and, where appropriate, to carry out full renal investigations in order not to leave the woman with persistent urinary damage.

Elliot E. Philipp

234. **Oxytocin and Renal Cortical Necrosis.**

By F. B. BYROM and O. E. PRATT. *Lancet*, **1**, 753–754. Apr. 11, 1959. 2 figs. 8 refs.

This paper from the Maudsley Hospital, London, gives an account of an experimental investigation into the vasoconstrictor activity of oxytocin with particular reference to its effect on the renal cortex. Using female rats sensitized with large doses of oestrogens it was found that intense renal ischaemia leading to massive cortical necrosis could be produced by a large dose of synthetic or natural oxytocin. The authors speculate on the possible part played by oxytocin in the production of renal cortical necrosis as seen clinically following concealed accidental haemorrhage.

J. M. Brudenell

235. **Childbearing in Cardiac Disease.** (Il parto nelle cardiopatiche.)

By E. DEBIASI. *Ann. Ostet. Ginec.*, **80**, 211. Mar. 1958.

The author mentions 273 deaths in women suffering from cardiac disease in association with pregnancy, out of a total of 6,752 such cases seen in the Obstetric Clinic at Bari during 30 years. Of the deaths, 23 per cent occurred in pregnancy, 16 per cent in labour, 40 per cent in the 12 hours after delivery and 21 per cent in the puerperium.

He gives the following recommendations for the management of these cases. During pregnancy consultation with a cardiologist is essential. Special care is needed in the management of pregnancy. Psycho-physical preparation for labour should be given. Induction of premature labour is needed only in exceptional cases. The expulsive period in labour should be shortened with forceps. All manœuvres should be performed with a minimum of trauma. Caesarean section should be performed for obstetrical indications only. In cases of severe cardiac disease, delivery by the vagina is to be preferred to Caesarean section.

Cardiac surgery may be performed as an emergency even during labour for cases of pulmonary oedema associated with mitral stenosis.

Josephine Barnes

236. **Serum Lactic Dehydrogenase in Pregnancy.**

By W. A. LITTLE. *Obstet. Gynec.*, **13**, 152–162. Feb. 1959. 6 figs. 25 refs.

Lactic Acid Dehydrogenase During Pregnancy and Puerperium.

By J. J. SMITH, E. D. SCHWARTZ and M. K. SCHWARTZ. *Obstet. Gynec.*, **13**, 163–165. Feb. 1959. 1 table. 5 refs.

In 75 normal pregnancies serum lactic dehydrogenase (LDH) was not elevated during any period of gestation. Normal labour was accompanied by LDH elevations in 18 per cent, many of which had placental infarction. In 40 per cent of Caesarean sections, patients developed transient LDH elevations post-operatively. Abruptio placentae was usually associated with increased levels of serum LDH.

It is thought that necrosis plays some role in serum enzyme elevations. The elevation noticed in the above cases may be associated with placental ischaemia, and the object of this study was to find a factor that might be utilized as a measure of "placental insufficiency". LDH may be pertinent to this goal in some degree.

In the second of the above two contributions on this subject it is pointed out that there is discrepancy in the literature on this subject, possibly due to different analytical methods. These authors found that LDH was slightly elevated in 18 per cent of 100 pregnant women and in all of 15 post-partum patients.

J. G. Dumoulin

237. **Serum Protein, Lipid and Lipoprotein Fractions in Normal Human Pregnancy.**

By E. K. SMITH, R. R. DE ALVAREZ and J. FORSANDER. *Amer. J. Obstet. Gynec.*, **77**, 326–334. Feb. 1959. 2 tables. 4 figs. 17 refs.

This study was undertaken in order to get a normal base line as a preliminary to a similar study in various disorders of pregnancy, especially toxaemias.

Blood samples were obtained 4 hours after a light breakfast from a 25-year-old normal primigravida on a liberal diet from the 5th week of pregnancy at monthly intervals till 36 weeks, when pregnancy ended spontaneously in the birth of a healthy child.

Total proteins fell from 7·40 g. per 100 ml. at 5 weeks to 7·29 g. per 100 ml. at 34 weeks, and albumin decreased from 55·3 per cent at 5 weeks to 41·0 per cent at 34 weeks. Alpha globulin increased from 4·7 per cent at 5 weeks to 5·9 per cent at 34 weeks, and alpha$_2$ globulin from 9·7 per cent at 5 weeks to 13·9 per cent at 34 weeks. Gamma globulin was unchanged, but beta globulin increased from 17·0 per cent at 5 weeks to 27·1 per cent at 34 weeks.

Cholesterol, both free and ester, and lipid phosphorus increased as pregnancy progressed, reaching their maxima at term. The percentage of alpha lipo-protein fell from 35·0 at 5 weeks to 18·4 at 34 weeks, but beta lipo-protein, which constitutes about 80 per cent of the total serum cholesterol, rose from 65·0 per cent to 81·6 per cent. The return to normal both of serum protein and serum cholesterol was very slow and took about 6 months which suggests that involution takes longer than the usually accepted 6 weeks.

F. J. Browne

238. **Abnormalities of Blood Coagulation During Pregnancy.** (Blutgerinnungsstörungen wahrend der Gestation.)

By B. ZSOLNAI. *Zbl. Gynäk.*, **81**, 356–367. Feb. 28, 1959. 2 tables. 3 figs. 28 refs.

During the five-year period 1953–1957, the author observed 67 cases of premature separation of the placenta. The bleeding was severe in 15, moderate in 19 and slight in 33. Evidence of toxaemia was present in only half of the cases. A haemorrhagic syndrome endangering life was present in 5 patients (7 per cent) of whom 3 were proved to be suffering from afibrinogenaemia. Two of these are described.

The author discusses the mechanism of defibrination. He repeated experimental work carried out by others, by giving a single intravenous injection of purified Coli-endotoxin filtrate to 6 pregnant rabbits. He found haemorrhages in the uterine cornua at the placental sites and multiple petechiae in almost all organs.

There were haemorrhages in the choriodecidual space which involved the myometrium. The histological and the macroscopic picture resembled that of a "Couvelaire" uterus. The blood did not coagulate even after 24 hours. The author failed to detect any fibrin clots in the small vessels and capillaries. He believes that the appearances were more suggestive of a toxic capillary damage and anaphylactoid reaction rather than of intravascular deposition of fibrin.

As a preliminary sensitizing dose of endotoxin is not required in the pregnant rabbit in order to produce the characteristic pathological changes, the author believes that the haemorrhagic syndrome is at least partly due to an altered reactivity of the organism in pregnancy.

Bruce Eton

239. **Hypofibrinogenaemia in Obstetrics.**

By E. L. TROTT. *S. Afr. med. J.*, **33**, 134–140. Feb. 14, 1959. 26 refs.

The author refers to the work of Dieckmann, Schneider and Maloney in the recognition of this condition and its treatment. The clotting mechanism is discussed. In 34 cases of concealed accidental haemorrhage at the Baragwanath Hospital there were 14 cases of hypofibrinogenaemia; 6 were toxic and 8 non-toxic. Amniotic embolism and missed abortion are discussed as causes. The rhesus factor is responsible only indirectly by causing intra-uterine death and retention of a dead foetus. Dextran may lower an already low plasma fibrinogen and pitocin may force thromboplastin into the circulation. The plasma-fibrinogen depletion theory and the thromboplastin, anaphylactoid and fibrinolysin theories are discussed. The hyper-acute, acute and chronic clinical manifestations are described. The 4 main tests used for diagnosis were the clotting time, the clot observation test, the topical thrombin test and prothrombin time confirmed by the plasma fibrinogen level. Thrombocytopenia is regarded as of grave import.

The treatment of missed abortion and retention of a dead foetus beyond 4 weeks may have to be reviewed. Pitocin should be used with care. In a series of 7 cases, fresh blood stopped the bleeding in 4. In the other 3 cases fibrinogen had to be given. Double or quadruple-strength plasma is an excellent substitute. In some cases massive doses (10 g.) of fibrinogen are necessary. Induction of labour after correction of the clotting mechanism is advised. The place of Caesarean section is controversial and it should only be done after a preliminary trial by rupturing the membranes. Indications for hysterectomy rarely occur. Fifteen cases are described.

L. J. Abramowitz

240. **Unusual Ovarian Changes (Hyperthecosis) in Pregnancy.**

By M. J.-G. Lynch, P. R. Kyle and P. Bruce-Lockhart. *Amer. J. Obstet. Gynec.*, **77**, 335–346. Feb. 1959. 11 figs. 25 refs.

Three cases are described of pregnancy in association with ovarian hyperthecosis resembling in their gross and microscopic features those of the Stein-Leventhal syndrome. In two of the cases there were signs of masculinization—hoarse voice, large clitoris and hirsutism. In the third there was severe hyperemesis at 5 months followed by fatal acute yellow atrophy of the liver. There were no definite signs of virilism in this case.

The authors accept the view of Culliner and Shippel that the ovarian theca cells are the source of androgenic hormone, and believe that the theca cells may be responsible for the slight masculinization that may appear in normal pregnancy.

F. .Browne

241. **Histoplasmosis in Pregnancy.**

By M. Sabin and N. M. Brown. *Obstet. Gynec.*, **13**, 218–222. Feb. 1959. 4 figs. 13 refs.

Histoplasmosis is an infectious disease caused by an intracellular, parasitic fungus. It may have a varied clinical picture ranging from a benign primary pulmonary phase to a severe generalized form involving the reticulo-endothelial system. The benign pulmonary infections are usually asymptomatic and are the most common. Infection may, however, begin in the mouth, larynx, pharynx and ears, and these show local necrotic ulcerations and enlargement of the regional lymph nodes. The progressive disease is characterized by splenomegaly, hepatomegaly, emaciation, irregular pyrexia, leucopenia, and anaemia. The disease is usually self-limiting but occasionally chronic. There is, as yet, no specific treatment.

The authors report two cases with asymptomatic pulmonary lesions diagnosed by chest X-ray in pregnancy and confirmed by a positive histoplasmin skin test. They describe the diagnostic radiological features.

J. G. Dumoulin

242. **Ectopic Pregnancy: A Review of 481 Cases.**

By J. T. Armstrong, S. H. Wills, J. Moore and A. E. Lauden. *Amer. J. Obstet. Gynec.*, **77**, 364–370. Feb. 1959. 6 tables. 2 figs. 1 ref.

Ectopic Pregnancy: A Review of Fifty Cases at Tripler U.S. Army Hospital.

By F. L. Soisson and J. P. Moran. *Amer. J. Obstet. Gynec.*, **77**, 352–363. Feb. 1959. 11 tables. 22 refs.

In the series of 481 cases there were 3 deaths. There were 11 cases of repeated tubal pregnancy and one of these patients had a third tubal pregnancy. Shoulder or neck pain was present in 62 patients (12·8 per cent). In 3·6 per cent pain was completely absent anywhere. A palpable mass was described in only 67 per cent. Abdominal tenderness was noted in 93 per cent and rebound pain in 40 per cent. Culdocentesis was used in 308 (64 per cent) and in 34 of these (11 per cent) it did not produce blood. Posterior colpotomy was used in diagnosis of 38 cases (8 per cent) in one of which the rectum was entered. The ectopic pregnancy was proved vaginally in 15 cases, in 3 of which vaginal hysterectomy was done. Culdoscopy was not used once. Culdocentesis is considered an invaluable aid in diagnosis and reduces the time of observation before treatment. A negative result does not eliminate ectopic pregnancy and one death resulted from presuming that it did. At autopsy there was 3,000 ml. of blood in the peritoneal cavity.

Soissons and Moran also regard culdocentesis as a most valuable aid in diagnosis, though a positive result was obtained only 83 per cent of the ectopics in their series in which it was done. They also regard posterior colpotomy lightly but do not consider that it should be used as means of removing the pregnancies. Appendicectomy is ruled out as dangerous when there is free blood as a culture medium in the abdominal cavity.

F. J. Browne

LABOUR

243. **Remarks on the Mechanism of Labor.**

By S. A. Cosgrove. *West. J. Surg., Obstet. Gynec.*, **67**, 5–9. Jan.–Feb. 1959. 4 refs.

The author describes the usually accepted views on the mechanism of a vertex birth but makes a plea for the re-definition of the first stage by recognizing engagement of the head as essential for its completion; if the head is not engaged, forceps extraction should not be attempted even though the cervix is fully dilated; by this means delivery for mother and baby would be much safer.

D. C. A. Bevis

244. **Relationship Between Strength of Foetal Membranes and Spontaneous Rupture of the Fore-Waters.** (Eihautfestigkeit und Blasensprung.)

By E.-L. NÖLKE. *Zbl. Gynäk.*, **81**, 472–479. Mar. 21, 1959. 4 tables. 6 figs. 7 refs.

The author tested the strength of the foetal membranes in 536 cases. The method consisted in mounting the membranes on a pressure chamber and exposing them to various degrees of tension by means of a column of water at room temperature. It was found that the pressure at which the membranes ruptured was inversely proportionate to the speed at which it was applied. The lower the initial tension, the greater was the resistance to rupture caused by an increase.

The membranes were found to be strongest in cases where they had ruptured prematurely and weakest in those in which they had ruptured late in labour. This is partly attributed to the fact that a persistent bag of forewaters is mostly lined by amnion only and that the strength of the membranes decreases with the degree of separation of the chorion from the amnion.

The author concludes that premature rupture is hardly ever due to primary weakness of the membranes. Similarly, delayed rupture is not solely due to abnormal strength of the membranes.

Bruce Eton

245. **Abdominal Decompression in Pregnancy and Labour.**

By O. S. HEYNS. *Med. Proc.* (*Johannesburg*), **5**, 121–135. Mar. 21, 1959. 3 tables. 3 figs.

The author claims that Dick Read's relaxation and hypnotism causes relaxation of the abdominal wall. He considered that reduction of the atmospheric pressure outside the abdomen might relax the abdominal musculature and perhaps allow the abdomen to bulge forward. The upper abdominal wall does move forward during a first stage contraction. If the abdominal wall did not force the uterus back again the so-called retraction would be highly efficient. A decompression apparatus consisting of a chair, a pump, a plastic air-tight suit and an incompressible spicer made of fibre glass has been devised. Decompression tends to increase the length of the contraction and also its strength. Yet patients suffer very much less with its use. A pressure drop of 40–50 mm. Hg is the level normally used during contractions. Some patients are quite happy about dropping this to 100 mm. Hg or even lower. Seven cases are reported in detail to show certain aspects of decompression. Only 2·4 per thousand spontaneous first labours had a first stage of under 5 hours, but with this apparatus 72 per cent of cases were delivered in less than 5 hours. As far as the parturient is concerned relief of pain is much more important than reduction of the duration of the first stage. In many cases decompression produced 80–100 per cent analgesia.

L. J. Abramowitz

246. **Delayed Post-partum Haemorrhage Due to Noninvolution of the Placental Site.**

By H. L. GAINEY. *West. J. Surg. Obstet. Gynec.*, **67**, 76–79. Mar.–Apr. 1959. 11 refs. 3 figs.

A case is described, from the University of Kansas, where there was repeated severe haemorrhage after a normal delivery. There was no evidence of retained pieces of placenta or blood coagulation defects and treatment consisted of uterine packing and massive blood transfusions.

The author reviews the literature on this condition in which the basic defect appears to be failure of involution over the placental site and stresses the diagnostic points of a large (12–16 weeks gestation) thin-walled uterus with its cavity distended with blood clots and the cervix widely open and patulous.

D. C. A. Bevis

ANAESTHESIA

247. **Fluothane for Obstetric Anaesthesia.**

By C. A. ALBERT, G. ANDERSON, W. WALLACE, E. E. HENLEY, A. W. WINSHEL and S. N. ALBERT. *Obstet. Gynec.*, **13**, 282–284. Mar. 1959. 11 refs.

Fluothane was used in routine deliveries as a substitute for trichlorethylene and also for Caesarean sections. The action of this anaesthetic is similar to that of chloroform, and both have similar properties. As an anaesthetic in obstetrics, fluothane produces marked uterine relaxation and, in most instances, excessive post-partum bleeding, and for this reason it should be used with great caution. Uterine tonus, however, did not seem to be affected when fluothane was used for curettage following abortion in the first 3 months of pregnancy.

J. G. Dumoulin

248. **Uterosacral Block.**

By W. J. SPANOS and J. C. STEELE. *Obstet. Gynec.*, **13**, 129–134. Feb. 1959. 7 tables. 14 refs.

The authors suggest that the combination of uterosacral nerve block with pudendal nerve block in labour offers a simple, efficient method of pain relief. A transvaginal pudendal block was first performed, using 1 per cent cyclaine. The uterosacral ligaments were then injected at 4 and 8 o'clock in each vaginal fornix with the tip of the needle just below the mucosa of the vagina, 8–10 ml. of solution being injected on each side. The blocks were performed at various times during the first stage of labour, the majority when the cervix was 4–8 cm. dilated. The duration of pain relief varied between 20 minutes and 3 hours, most lasting 60–90 minutes. The injection was repeated in some cases, and the majority

had some form of additional anaesthesia in the second stage, usually nitrous oxide. There was no clinical evidence of toxicity. Pain relief was good in the majority of cases. *J. G. Dumoulin*

PUERPERIUM

249. **Bowel Function During the Lying-In Period.**
By A. Bach and M. Ingerslev. *Acta obstet. gynec. scand.*, **38**, 88–92. 1959. 2 figs. 9 refs.

Bowel function was investigated in 411 puerperal women. Forty per cent of these patients who were allowed out of bed on the first day post-partum had spontaneous bowel movement daily following re-establishment of bowel function, as compared with 30 per cent of those allowed out of bed on the fourth day after delivery.

Spontaneous bowel movement occurred in 60 per cent of the women before the sixth day post-partum. The patients allowed out of bed on the first day had spontaneous bowel movement earlier than those who got up on the fourth day.

The authors suggest that routine treatment with cathartics during the puerperium is not justified, particularly if early ambulation is instituted. *N. Alders*

250. **Foetal Erythrocytes in the Maternal Circulation.**
By A. Zipursky, A. Hull, F. D. White and L. G. Israels. *Lancet*, **1**, 451–452. Feb. 28, 1959. 2 tables. 4 figs. 3 refs.

The authors have studied the blood of 42 puerperal women at the University of Manitoba, Canada. Using a special staining technique maternal blood smears were examined for foetal erythrocytes. Eleven (21 per cent) of the 42 women had foetal cells in their circulation, suggesting that transplacental passage of foetal blood is a common occurrence. *J. M. Brudenell*

INFANT

251. **Resuscitation of Stillborn Infants.**
By H. H. Epple and J. M. Sutherland. *Obstet. Gynec.*, **13**, 259–263. Mar. 1959. 16 refs.

The authors report a case in which during the course of a spontaneous delivery there was shoulder dystocia. The head of the infant became cyanotic. After 11 minutes the posterior arm was extracted, and at this stage the heart could not be heard on auscultation. Delivery was completed after 3 more minutes. The infant was intubated and artificial respiration given. When 3 minutes later no heart sounds were audible, the chest was opened through the left fifth intercostal space. The heart was flabby and dilated. Cardiac massage was started by rhythmic squeezing of the heart with the forefinger against the sternum from base to apex. After 3 minutes of massage, normal heart beats followed. Regular respiration started some minutes later. At 4 months, the infant seemed normal.

Spontaneous beating of the heart after cardiac arrest in such a case does not occur, so that this procedure would seem to be justifiable in selected cases. Such cases are possibly infants born after a shoulder arrest or by breech presentation after arrest of the aftercoming head with sudden cardiac arrest when the period of anoxia has been short. *J. G. Dumoulin*

252. **Obstructive Jaundice and Haemolytic Disease of the Newborn.**
By T. E. Oppe and T. Valaes. *Lancet*, **1**, 536–539. Mar. 14, 1959. 1 table. 3 figs. 10 refs.

The authors studied 117 cases of haemolytic disease of the newborn due to rhesus incompatibility at Southmead Hospital, Bristol. Sixty-three of these cases required exchange transfusion, 12 showing obstructive jaundice. Of the 4 neonatal deaths 3 were in the "obstructed" group. Infants were designated as showing obstructive jaundice if at the peak of the jaundice at least one-third of the total serum bilirubin was in the conjugated form.

It is contended that the obstructive lesion is not primarily hepatic cellular damage or biliary thrombosis but is related to the severity of the initial haemolytic process and is modified by treatment.

Early adequate exchange transfusion is the most important factor in management. The "obstructed" group do not show a higher incidence of kernicterus but may develop hypoprothrombinaemia.

Parenteral vitamin K is given as a prophylaxis against the latter whenever obstructive jaundice becomes apparent.

The authors conclude that these cases represent a definite clinical entity within the spectrum of disease caused by rhesus incompatibility. *J. M. Brudenell*

253. **Cord-Blood Findings in ABO Haemolytic Disease.**
By G. H. Tovey, E. M. Gillespie, J. Guy, T. Valaes, T. E. Oppe and F. J. W. Lewis. *Lancet*, **1**, 860–863. Apr. 25, 1959. 3 tables. 3 figs. 7 refs.

Haemolytic disease in the newborn is caused as frequently by ABO incompatibility as by rhesus antibodies. ABO haemolytic disease is fortunately mild in most cases, however, and the need for exchange transfusion infrequent. The authors studied a group of 575 babies born at Southmead Hospital, Bristol, in order to correlate cord-blood findings with clinical findings with a view to predicting more accurately the severity of ABO haemolytic disease. Six of the 575 babies showed clinical and laboratory evidence of ABO haemolytic disease. The only consistently reliable clinical sign was the development of jaundice within 24 hours (rhesus incompatibility having been excluded). Cord-blood examination in the 6 cases showed no consistent diagnostic feature. None of these cases required exchange transfusion but in 7 other cases outside the series described who did require transfusion the level of indirect bilirubin in the blood was found to be the most reliable guide in deciding when a transfusion was

necessary. A level of 25 mg. per 100 ml. was taken as the upper limit of safety, and the authors suggest that a rapidly rising serum bilirubin in the first 3 days of life is an indication for exchange transfusion, whereas if the serum-bilirubin level only reaches the danger zone at 5 or 6 days, the baby may be watched.

J. M. Brudenell

254. **The Value of Electroencephalography During Follow-Up Examination of Children Delivered by Obstetric Operations.** (Wert der Elektroenzephalographie bei Nachuntersuchung von Operations- (Kaiserschnitt-, Zangen- und Extraktions-) kindern.)

By Gy. György, F. Obal and J. Szenasy. *Zbl. Gynäk.*, **81**, 344–350. Feb. 28, 1959. 2 figs. 3 tables. 22 refs.

Of 2,730 children born in the course of three years, 280 were delivered by Caesarean section, forceps or extraction. Of these 158 were traced. One hundred attended for paediatric and neurological examination, including electroencephalography. Their ages ranged from 1 to 4 years.

Amongst 36 children delivered by Caesarean section, the EEG revealed minor lesions in 2 cases. Two similar cases were observed in 46 children delivered by forceps. Amongst 18 children born by extraction the EEG showed 1 case of gross cerebral damage.

Clinical neurological examination did not reveal any other abnormality in the 5 cases. It was pointed out that the follow-up will have to continue, as it is generally known that latent lesions may not necessarily give rise to clinical manifestations until much later in life.

The authors point out that electroencephalography has not so far been adequately studied and utilized in infants.

Bruce Eton

255. **Neurological Aftermaths in Children of Eclamptic Women.** (Die Eklampsie und später sich manifestierende neurologische Schädigungen der Nachkommenschaft.)

By I. Gavaller, E. Orosz and I. Sera. *Zbl. Gynäk.*, **81**, 713–719. May 2, 1959. 2 tables. 23 refs.

The authors studied a series of 418 women who had suffered from eclampsia between 1932 and 1955. During the 24 years there were 37,160 births. Ninety-six mothers attended for follow-up with 70 children. Both mothers and children were investigated from a general medical, neurological and psychiatric point of view. For the last the Binet-Simon test was used.

Neurological or psychiatric abnormalities were found in 23·9 per cent of 46 children over 3 years of age. Amongst 13 children under 3 years there was 1 case (9·1 per cent). A third group was considered separately where the child was born before convulsions occurred. There were 2 cases (15·4 per cent).

There was no significant evidence of a hereditary factor in any of the groups. In only one case of 4 epileptic children was the mother suffering from the same condition. There was no direct relationship between the severity of the eclampsia and the neuro-psychiatric changes in the child, yet the authors attribute these changes to hypoxia or anoxia. They advise Caesarean section for cases of pre-eclamptic toxaemia which deteriorate or fail to improve with conservative management.

Bruce Eton

256. **Incidence of Congenital Malformations in Dresden.** (Missbildungsfrequenz in Dresden.)

By R. Hohlbein. *Zbl. Gynäk.*, **81**, 719–731. May 2, 1959. 5 tables. 8 figs. 66 refs.

The author reports on a series of 748 congenital malformations observed in 129,382 births between 1921 and 1958, an incidence of 0·58 per cent. There was a significant rise in the incidence between the years 1946 to 1950, attributed to the effects of the war and post-war periods. 43·7 per cent of all malformations were neuro-ectodermal, and 40·4 per cent were hereditary. The series is limited to malformations detected immediately after birth and does not include any developmental abnormalities discovered at post-mortem examinations, [This limits the value of the statistical data.]

From the prophylactic point of view the author makes the following recommendations: marriage guidance should include advice regarding diabetic and pre-diabetic syndromes; women should be instructed not to use contraceptive and abortifacient agents; attempts to preserve pregnancy in spite of prolonged bleeding should be abandoned; childbearing should not be postponed until after the fortieth year. He advises thorough and prompt treatment of any febrile diseases, particularly virus infections; protection of expectant mothers against contact with cases of rubella; early search for toxoplasmosis, listeriosis, Rh-incompatibility and syphilis; avoidance of ultra-violet therapy; avoidance of deficiency or excess of vitamins A, D and E; avoidance of treatment with sex hormones, cortisone, cytostatic and anti-thyroid agents and of overdosage with insulin; and limitation of radiological investigations in young women, particularly during the early months of pregnancy, when foetal tissues are most sensitive to the effects of radiation.

Bruce Eton

257. **The Association of Foetal Abnormalities and the Administration of Oestrogens During Early Pregnancy.** (Fehlbildungen nach Follikelhormonen beim Menschen.)

By H. Uhlig. *Geburtsh. u. Frauenheilk.*, **19**, 346–352. Apr. 1959. 3 figs. 7 refs.

Three cases are reported of foetal malformation, oestrogens having been administered during the early weeks of pregnancy (in 2 cases in an attempt to procure an abortion). The first baby was born at full-term by the breech. It was hydrocephalic and had a large thoraco-lumbar myelomeningocele. There was also gross talipes. An unknown quantity of an unidentified oestrogen had been given for 8 days from the 6th week of pregnancy. The second patient had been given 6 mg. of dienoestrol daily from the 5th–8th week of her pregnancy. She was delivered at full-term of an hydrocephalic infant, with a thoraco-lumbar myelomeningocele. Both lower limbs

were grossly deformed. In the third case 1·5 mg. of dienoestrol were given for 14 days during the second month of pregnancy. The baby was hydrocephalic, both lower limbs were absent and there was a congenital amputation of the right arm at the elbow.

The author argues that the use of oestrogens in early pregnancy and the congenital abnormalities observed were cause and effect and not coincidental. The time of administration of the oestrogen would agree with the embryological history of these abnormalities. He has attempted to confirm this hypothesis and states that if oestrogens are administered to rats in early pregnancy severe foetal damage is produced. Details of these experiments are not given.

Peter J. Huntingford

258. **Ano-rectal Malformations.** (Malformazioni ano-rettali.)

By G. C. RONCHETTI and U. BALDI. *Ann. Ostet. Ginec.*, **80**, 473. May 1958. 7 figs. 36 refs.

The pathology, embryology and classification of congenital malformations in the anorectal area are discussed with reference to the literature.

The authors described eleven personal cases. These embody almost all known ano-rectal anomalies. Accurate diagnosis is very important and also the choice of the best time for operation.

Of the numerous procedures described the abdomino-perineal approach is the one now preferred, and is most likely to give the best functional result.

Josephine Barnes

259. **Oesophageal Atresia with Tracheo-Oesophageal Fistula.** (Atresie esofagee con fistola tracheo-esofagea.)

By G. C. RONCHETTI. *Ann. Ostet. Ginec.*, **80**, 459. May 1958. 6 figs. 26 refs.

The author describes two cases of congenital tracheo-oesophageal fistula which were successfully treated. He outlines the embryology of the condition and describes the twelve different varieties encountered.

The first case presented as a tracheo-oesophageal fistula with atresia of the oesophagus. This was demonstrated radiologically after clinical features such as cyanosis after feeding had led to the diagnosis. Thoracotomy was performed; the fistula was closed, an anastomosis was made in the oesophagus and the pleural cavity closed. Feeding by mouth was begun 36 hours after the operation. The post-operative result was satisfactory both clinically and radiologically.

The second case was similar except that the anastomosis was more difficult because the two stumps of the oesophagus were widely separated. An indwelling oesophageal catheter was used for feeding, for the first five days. The clinical and radiological result was ultimately satisfactory.

Specialized centres for the treatment of major congenital deformities are necessary if the best results are to be achieved.

Josephine Barnes

GYNAECOLOGY

260. **Account of 9 Years' Experience in the Berlin Women's Advisory Clinics.** (Erfahrungen aus 9 jähriger Tätigkeit in den Berliner Frauenberatungsstellen.)

By I. BRANDT. *Zbl. Gynäk.*, **81**, 414–436. Mar. 14, 1959. 23 tables.

The author presents the results of a thorough study and evaluation of a series of 4,271 patients who attended for consultation at 3 West Berlin women's advisory clinics between 1947 and 1956. 89·1 per cent of the women were between 20 and 45 years of age. Eighty-three per cent were, or had been, married. Among the married women there was a higher proportion in the lower income groups than among single women. Only 19·9 per cent of patients belonged to the poorest classes.

Reasons for attendance were mainly contraception (68·9 per cent). The others attended because of gynaecological complaints, request for termination of pregnancy, coital problems, matrimonial problems, infertility, and legal questions. There was a comparatively high proportion of single (including engaged) women amongst those attending for advice on sexual matters, indicating a lack of instruction by their parents and teachers; in some cases, however, a eugenic question was raised, such as epilepsy, haemophilia, etc.

Whereas in Asiatic countries birth control is an urgent public demographic problem supported by the State, in Western countries it is a concern of the individual aiming at responsible and sound family planning.

The incidence of previous pregnancies among both married and unmarried groups was the same (47 per cent). It is for this reason that the author feels that contraception clinics should not be restricted to married women; if instruction and advice is made available to all women a significant contribution may be made towards reducing the number of criminal abortions and children handicapped by illegitimacy. Particularly in the case of unmarried women the scope of the consultation includes instruction and moral guidance, helping to develop before marriage a sense of responsibility regarding reproduction, marital partnership, realistic family planning, spacing of pregnancies and rearing of children. The author makes a plea for the improvement of sex education of young people by their parents and teachers. This must include training for a sense of responsibility and clear attitude towards problems of sex.

She discusses the indications for and methods of contraception and concludes that the vaginal occlusive pessary used with a spermicidal preparation is the best available to the female.

Bruce Eton

261. **Paravaginal Haematomata.**

By B. BLOCH. *S. Afr. med. J.*, **33**, 241–243. Mar. 21, 1959. 3 figs. 12 refs.

The author has reviewed 14 case histories of this condition in order to assess the most satisfactory mode of treatment. General and anatomical classifications are presented. The incidence is probably between 1:500 and 1:2,000, but many small tumours may pass unnoticed. The paravaginal space and vaginal venous

plexus with its anastomotic vessels are described. Haematomata may be above or below the levator muscle, and they may be small or very extensive. Their development may be slow or rapid. Rupture of a vessel is due to trauma of childbirth or other trauma, but improper haemostasis, pressure necrosis of an affected vessel, blood dyscrasias, vulval varicosities or vascular changes due to pre-eclampsia may be predisposing causes. The chief symptom is pain and the main sign is the presence of a mass either below or above the levator ani. If bleeding is severe there may be shock and anaemia and urinary symptoms. Treatment may be expectant or surgical. In 9 cases treated by incision and drainage the average stay in hospital was 6 days and 1 patient was morbid. In 5 cases treated conservatively the average hospitalization was 11 days and 3 patients were morbid. Primary incision and drainage appeared to be the method of choice.

L. J. Abramowitz

DISORDERS OF FUNCTION

262. **Clinical Manifestations of Hypometabolism in Women.**

By H. M. Foster. *Amer. J. Obstet. Gynec.*, **77**, 130–137. Jan. 1959. 2 tables. 13 refs.

Hypometabolism was diagnosed in 13 per cent of 800 women attending a gynaecological clinic. The mean age was 45 years. The main symptoms were chronic fatigue, present in 87 per cent, enlarged thyroid gland (87 per cent), dry hair (81 per cent), dry skin, hypersensitivity to cold, oedema, depression, and "pelvic congestion syndrome" with pelvic pain and adnexal tenderness. Almost all the patients responded well to liothyronine which is more effective than desiccated thyroid.

F. J. Browne

263. **Amenorrhoea Associated with Retention of Fertility.**

By L. Ph. Bengtsson and C.-A. Ingemansson. *Acta obstet. gynec. scand.*, **38**, 62–67. 1959. 1 fig. 15 refs.

This is a detailed report, coming from Lund, Sweden, on a girl who developed persistent amenorrhoea following a head-injury at the age of 15. However, cyclical ovarian and endometrial changes continued, as demonstrated by repeated endometrial biopsies and vaginal smears. She married at the age of 23 and, whilst the amenorrhoea persisted, she gave birth to 4 children during the ensuing 8 years.

N. Alders

264. **The Progestational Effects of 17-alpha-ethinyl-19-nortestosterone.** (Sugli attributi progestazionali del 17-alfa-etinil-19-nortestosterone.)

By G. Tronconi. *Ann. Ostet. Ginec.*, **80**, 283. Mar. 1958. 29 figs. 36 refs.

Clinical results of treatment of cases of secondary amenorrhoea and of hyperoestrinization with the new synthetic progestogen 17-alpha-ethinyl-nortestosterone are described.

In 10 out of 13 cases of secondary amenorrhoea treatment with 5 mg. twice daily for 10 days, following preliminary treatment with conjugated natural oestrogens produced uterine bleeding. Progesterone activity was noted by vaginal smears which showed marked luteal change. Success was also achieved in cases of hyperplasia of the endometrium.

The new progestogen was also used for the treatment of threatened abortion. Twenty-six cases were treated; 14 in hospital and 12 ambulatory. In all a satisfactory result was obtained and pregnancy continued.

Josephine Barnes

265. **Dysfunctional Uterine Bleeding: The Relationship of Microscopical Observations to Treatment.**

By P. N. Shah and M. J. Dave. *J. Obstet. Gynaec. India*, **9**, 226–235. Mar. 1959. 4 figs. 10 refs.

Dysfunctional uterine bleeding is taken as abnormal bleeding from a uterus in which there is no neoplastic, inflammatory or chorionic lesion. In such cases, it was assumed that the bleeding was due to an imbalance of oestrogens and progesterone in the circulation.

In 27 cases of dysfunctional bleeding, the endometrium was taken for biopsy, and the vaginal cytology was studied in an attempt to assess the degree of imbalance in the circulation of oestrogens and progesterone. An oestrogen preponderance was diagnosed by a state of cystic glandular hyperplasia in the endometrium associated with 40 per cent or more cornified cells in the vaginal smear.

In all such cases testosterone was given, and the dosage was guided by the degree of cornification of the vaginal smear. It is suggested that this is an accurate way of evaluating a treatment which is useful in young women with dysfunctional bleeding due to a preponderance of circulating oestrogens.

John McKiddie

266. **Trial with Local Injection of Estradiol Benzoate: A Preliminary Report of its Effect on Hypoplasias of Uterus and Crystallization Phenomenon of Cervical Mucus.**

By J. N. Karande and R. R. Gajkhandh. *J. Obstet. Gynaec. India*, **9**, 217–225. Mar. 1959. 4 figs. 10 refs.

A small series of cases of uterine hypoplasia were treated by intra-cervical injection of oestradiol benzoate, and the results are tabulated. It is assumed that under the influence of oestrogens in the circulation, the uterus has reached adult size before the menarche, but that a certain number of uteri remain unresponsive and infantile, even in the presence of a normal menstrual cycle. Twenty-nine cases were taken in which the uterine length was less than 8 cm. Each patient was examined monthly, when the uterine length was measured, the cervical mucus studied, and an endometrial biopsy taken. Oestradiol benzoate was injected once a month intracervically at the commencement of the cycle.

In 12 cases in which ovulatory cycles were occurring, the maximum uterine length normally occurred premenstrually. In 14 cases there was no secretory endometrium obtained and the cycle was presumed anovular.

In these the maximum uterine length was around mid-cycle. In 3 cases of primary amenorrhoea in which no endometrium was obtained on curettage, no appreciable change occurred in the size of the uterus at any time.

If intra-cervical oestrogens were given the average increase in length of the uterus was 0·84 cm. in all cases, the increased length being more marked in the 3 cases of primary amenorrhoea than in the others.

In normal ovulatory cycles, oestradiol benzoate did not change the picture of crystallization in the cervical mucus. In anovulatory cycles, where crystallization was atypical, injection produced a transient change of the crystals to a normal pattern. *John McKiddie*

267. **The Effect of the Administration of Lipoid Extracts of the Diencephalus on the Genital Apparatus of Female Rats.** (Gli effetti della somministrazione di un estratto lipoideo di diencefalo sull'apparato genitale della ratta.)

By G. REMOTTI. *Ann. Ostet. Ginec.*, **80,** 259. Mar. 1958. 14 figs. 24 refs.

Female rats have been injected with a lipoid extract of the diencephalus daily for periods of 5 to 13 days. The result has been a powerful activity of the ovaries with endometrial hyperplasia. The secondary endometrial changes do not appear in the ovariectomized animal.

The possible mechanisms of this are discussed. It is suggested that there is direct action of diencephalic extracts on the ovaries without the intermediate agency of the anterior pituitary. *Josephine Barnes*

268. **A Rare Case of Pseudo-Hermaphroditism Treated with Surgery and Hormones.** (Ein seltener Fall von Pseudohermaphroditismus operativ and hormonal behandelt.)

By J. PRIBRSKY. *Zbl. Gynäk.*, **81,** 666–675. Apr. 25, 1959. 13 figs. 22 refs.

This is a detailed account of an individual of 22 years who had been brought up as a girl and who had clearly displayed feminine propensities since childhood. She had however never menstruated, but had noticed by the age of 17 that her external genitalia differed from those of other girls. She associated with men since the age of 18 and coitus had been attempted on a number of occasions.

On gynaecological examination the patient was found to have a male type of chest and breasts, a mons veneris, an organ which resembled a penis, two "labia" containing swellings resembling testes. The urethra opened 3 cm. from the tip of the "clitoris", and was grossly dilated, permitting the introduction of 2 fingers into the bladder. The vestibule had a depth of about 2 cm., and led into a narrow rudimentary vagina. The pitch of the speaking voice lay between the average of the male and the female. 17-ketosteroid excretion averaged 11·4 mg. per cent. Intravenous pyelography and perirenal insufflation did not reveal any abnormality.

After careful assessment of the psychological implications and taking into consideration the patient's strong desire that her external genitalia should be of the female type, one gonad and thereafter a second gonad were removed and found to be rudimentary testes. Part of the "penis" was amputated so as to reduce it to the size of a clitoris. Exploratory laparotomy did not reveal any internal genitalia.

Hormonal treatment consisted in repeated injections of long-acting oestrogen (Ovocyclin). When the patient was seen a few months later, she looked much more feminine and felt so. Her external genitalia looked typically female. Coitus was taking place regularly. Two years later the vagina had grown to a length of 9 cm. and admitted two fingers, and the diameter of the urethra had returned to normal. The patient had been happily married for a year.

[Chromatin studies are not mentioned in this paper. The interesting history would suggest that in cases of male pseudo-hermaphroditism the upbringing and the psychological conditioning may be more important considerations when deciding on treatment than the type of gonad.] *Bruce Eton*

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

269. **A New Method of Registration and Statistical Evaluation of Clinical Material.** (Ein neues Verfahren der Registrierung und statistischen Auswertung eines klinischen Krankengutes.)

By D. WAGNER and H. STEGMANN. *Zbl. Gynäk.*, **81,** 378–385. Mar. 7, 1959. 5 tables. 3 figs. 9 refs.

The authors find the punch-card system of indexing unsuitable for small numbers (200 or less), as it necessitates special equipment and non-medical assistance, and delays the evaluation of the material by extensive and time-consuming preliminaries. They introduced a synoptic system for cancer statistics. This consists of an index card divided into 290 rectangular fields: there are 29 general categories arranged horizontally, each with 10 subdivisions, arranged vertically. A system of coloured riders, clipped to the upper edge of each column indicates the findings relating to each category and permits a selection without removal of the card from its box. For each type of neoplasm a card of a different colour is used.

The advantage of this system is that the card itself provides all the relevant data without the necessity of a key, and allows the uninitiated reader to reconstruct the case at a glance. With practice the reader learns to spot certain recurring combinations of riders which leads to the recognition of previously unsuspected correlations.

In a review of the gynaecological cancers of 1956 the authors illustrate the speed with which statistical data can be extracted. *Bruce Eton*

270. **Detection of Gynecological Cancer by Fluorescent Microscopy.**

By W. SUSSMAN. *Obstet. Gynec.*, **13,** 273–277. Mar. 1959. 8 figs. 8 refs.

The acridine-orange procedure as a two-colour fluorescent microscopy test has been applied by the

author to detect gynaecological cancer. In smears stained by this method there is increased fluorescence of atypical and malignant cells. Acridine-orange has a specific affinity for the two nucleic acids present in normal and malignant cells, but the latter have a higher content of ribonucleic acid usually, and thus stain more intensely, showing a more brilliant fluorescence.

The technique of staining takes 12 minutes and the scanning 3 minutes for normals. This might therefore be a useful and rapid diagnostic procedure for mass screening. *J. G. Dumoulin*

271. **Follicle-Stimulating and Lutein-Stimulating Action on the Ovary in a Case of Hydatidiform Mole. A Discussion as to the Origin of this Action.** (De l'action folliculo-stimulante et lutéo-stimulante sur l'ovaire au cours d'une mole hydatiforme.)

By J. Seguy, P. Prunier and —. Bailly-Salin. *Gynéc. Obstét.*, **57**, 490–502. 1958. 3 figs. 36 refs.

The authors' practice in all cases of hydatidiform mole is abdominal evacuation of the mole by hysterotomy. This allows them to carry out a full laparotomy with observation of the ovaries. They claim that it also ensures that the whole of the uterus is completely evacuated and that this evacuation can be checked visually, and also that there is no risk of leaving a piece of tissue in a destruans mole inside uterine muscle.

In the course of one of these operations, they noticed that the ovaries were enlarged to the size of a human fist and that they contained enlarged Graafian follicles and also large luteal follicles; they took sections from the two types of follicle for microscopy.

The presence of the two different types of follicle led to a discussion of how and from where the follicle stimulating hormones arise. They come to no firm conclusion, but discuss the theories that there may be but one single stimulating factor, or two stimulating factors, or three stimulating factors, the three being follicle stimulating hormone, luteinizing hormone, and luteotrophic hormone. They estimated the follicle stimulating hormone in the fluid of one of the cysts and found it contained over 1,000 international units per litre. A month and a half later they repeated the estimation, this time on cyst fluid obtained by the vaginal route, and found it to contain 140 i.u. per litre. Before the laparotomy the urine was found to contain more than 500,000 i.u. of prolan B per litre, and a month after the operation between 5,000 and 50,000 i.u. per litre. Four months later there was less than 1,000 i.u. per litre.

They conclude that the prolans, and particularly prolan B, are more important than the other hormones and they feel that the solution of the problem of hypophyseal hormones is not far distant, but must be worked at much more fully.

[They failed to show, however, the difference between the prolans and the hypophyseal hormones and where the origin of prolans differs from that of hypophyseal hormones, so the problem is more complex probably than the simple solution of whether there are 1, 2 or 3 hormones at work in the normal menstrual cycle and in the hormonal changes accompanying hydatidiform mole.] *Elliot E. Philipp*

272. **Sub-acute Pulmonary Hypertension Due to Chorionepithelioma.**

By K. D. Bagshawe and W. D. W. Brooks. *Lancet*, **1**, 653–658. Mar. 28, 1959. 5 figs. 22 refs.

The authors report 4 cases of subacute pulmonary hypertension due to the occlusion of pulmonary arteries and arterioles by chorionepitheliomatous emboli. In two cases the diagnosis was confirmed at post-mortem. No growth was present in the uterus itself in one of these. In the remaining two cases the diagnosis was made on the basis of a greatly increased output of urinary gonadotrophins, and the patients concerned have shown a good response to treatment with anti-folic acid and anti-purine drugs in high intermittent dosage. The authors emphasize the importance of excluding the presence of a chorionepithelioma (by gonadotrophin estimations since curettage may be negative) in any woman of menstrual age who develops the features of subacute pulmonary hypertension. *J. M. Brudenell*

273. **The Multicentric Origin of Carcinomas of the Female Anogenital Tract.**

By W. Newman and J. K. Cromer. *Surg. Gynec. Obstet.*, **108**, 273–281. Mar. 1959. 8 figs. 26 refs.

In this report from Washington 6 cases of combined epidermoid carcinoma of the vulva and cervix are described. These are considered to provide further support for the multicentric "field" origin theory of cancer.

The youngest patient was 27 years of age, the oldest 80. Three patients were treated initially for invasive epidermoid carcinoma of the vulva and 3 for *in situ* epidermoid carcinoma and leucoplakia of the vulva. The first microscopic evidence of cervical carcinoma in these 6 patients was obtained 60, 15, 7, 31, 50 and 18 months respectively from the date of diagnosis of the vulval disease.

There are direct clinical applications to be derived from this group of cases and from the concept of the multicentric or "field" origin of cancer as applied to an organ, paired organs or "organ systems". The findings in these women suggest that patients with lesions of the anogenital area (vulva, vagina and perianal skin) whether reported as Bowen's disease, leucoplakia, pre-invasive carcinoma, carcinoma *in situ* or invasive epidermoid carcinoma should routinely have a biopsy of the cervix; and further, that patients who have had either *in situ* epidermoid carcinoma or invasive epidermoid carcinoma of the cervix should be followed closely for signs of new primary tumours of the vulva, vagina and perianal skin areas.

The possibility that many lesions often described as recurrences or metastases are in fact persistent or new disease in previously sensitized fields is discussed.

The authors emphasize that the multicentric "field"

origin theory is not to be misconstrued as a plea for extending the scope of surgery or increasing the number of prophylactic procedures but rather as a stimulus to more frequent, systematic, periodic post-operative examination of patients with particular attention to that organ, paired organ or "organ system" in which the first primary carcinoma has developed.

John P. Erskine

274. **The Occurrence of Pseudoxanthoma Cells in the Stroma of Adenocarcinomata of the Uterine Body.** (Über das Vorkommen von Schaumzellen im Stroma von Adenocarcinomen des Corpus Uteri.)

By H. A. KRONE and G. LITTIG. *Arch. Gynäk.*, **191,** 432–436. 1959. 1 table. 2 figs. 8 refs.

Foam or pseudoxanthoma cells are often present in areas of chronic suppurating inflammation representing a reaction of the connective tissues to the infection. They are, however, rarely found at sites other than the female genital tract. Theories as to their derivation include local cholesterol storage, local tissue changes, and vascular congestion since they also occur in the superficial layers of adenocarcinomata of the uterine body around congested capillaries.

The authors investigated 317 histological sections of adenocarcinomata of the uterine body and 72 sections of adenocarcinomata of the cervix collected from 8,597 histological sections prepared between 1955–1957. Pseudoxanthoma cells were present in about 13 per cent of cases in cancer of the body patients, occurring in most instances in well differentiated adenocarcinomata. These cells were usually found in well-established acini, where they were arranged in nests within the papillae or the superficial layers of the tumour. In the 72 sections of cervical adenocarcinomata no foam cells could be demonstrated; in cases of adenocarcinoma corporis et cervicis, even when foam cells were found in the body of the uterus, they did not seem to be present in the cervix. The occurrence of foam cells did not appear to be related to the type of tumour but rather to the sensitive reaction of the endometrial stroma to minimal stimuli during the growth of the tumour. *Erica Wachtel*

275. **Contribution to the Extended Use of Vaginal Cytology, by Means of Dry Fixation.** (Beitrag zur breiteren Anwendung der Vaginalzytologie durch eine Trockenfixierung.)

By H. F. BUCHHOLZ. *Zbl. Gynäk.*, **81,** 498–501. Mar. 28, 1959. 1 table. 2 figs. 10 refs.

The current method of fixing vaginal smears in alcohol-ether has the disadvantage that the specimen cannot be transported by post and that the material is highly inflammable. This tends to limit the practical application of vaginal cytology to the immediate vicinity of the laboratory.

The author, in a study of 1,829 smears, successfully tested the method of fixation in acetone described by Sagi and Mackenzie (*Amer. J. Obstet. Gynec.*, 1957, **73,** 437). With this method of fixation the smear is allowed to dry and can easily be sent through the ordinary post.

Details of the procedure and of a modification of the Papanicolaou staining technique are given.

Bruce Eton

276. **Comparative Cytology by Optical Electron Microscopy of Normal and Pathological Cervical Squamous Epithelium.** (Cytologie comparée en microscopie optique et électronique de l'épithélium pavimenteux cervical normal et pathologique.)

By R. MORICARD, N. HINGLAIS-GUILLAUD and R. CARTIER. *Gynéc. Obstét.*, **57,** 453–489. 1958. 2 tables. 17 figs. 68 refs.

In this paper histological appearances under the ordinary microscope are compared with those under the electron microscope. Three specimens were of normal cervical epithelium, one of a benign mucous polyp, one of a "dysplasia", one of a leukoplakia and two of cancers. One hundred and sixty electronic photomicrographs were taken. The work was done by collaboration between the Laboratory of Electronic Microscope and Cancer Research at Villejuif, the Gynaecological Clinic of the Faculty of Medicine of the University of Paris, and the Laboratory of Hormonology and Experimental Cytology of the Broca Hospital, Paris.

The first part of the paper consists of a review of the literature and a description of certain terms used, such as mitochrondia, ergastoplasm and the zone of Golgi.

The second part consists of a very full description of the material and techniques used for taking the specimens, fixing them, cutting them and preparing them, and the third and major part of the paper is concerned with comparing the results of the appearances under the two systems of microscopy.

This paper is clearly of the greatest interest to pathologists who are concerned with advanced microscopy and especially to research workers on the cell structure in carcinoma of the cervix. *Elliot E. Philipp*

277. **Results of Treatment of Carcinoma of the Cervix During the Years 1947 to 1952.** (Ergebnisse bei der Behandlung des Kollumkarzinom in den Jahren 1947 bis 1952.)

By K. A. HÜTER and H. G. MÜLLER. *Zbl. Gynäk.*, **81,** 531–536. Apr. 4, 1959. 8 tables. 19 refs.

The authors review a series of 276 cases of carcinoma of the cervix. The primary treatment for Stages I and II was Wertheim's hysterectomy followed by deep X-ray therapy. Pre-operative radium was never used, but cases regarded as inoperable or unsuitable for surgery were treated with radium and X-ray therapy. The absolute 5-year cure rate was 40·9 per cent. The relative cure rate for Stage I was 75·9 per cent, Stage II 48·3 per cent, Stage III 23·2 per cent and Stage IV 0 per cent.

The incidence was maximal between 40 and 60 years and the results of treatment were better in patients under the age of 50, which may be partly due to the diminished expectation of life in older women.

There was a high incidence of fistulae. In 2 of 16 women a vesico-vaginal fistula was present before treatment was begun, and in the remaining 14 there was carcinomatous invasion of the vesico-vaginal fascia. Sixteen women had a recto-vaginal fistula; one of these was present before treatment. In 13 of these women the recto-vaginal septum was invaded by the carcinoma. There were 3 cases of uretero-vaginal fistula attributable to surgery. They were cured after re-implantation of the ureter.

Bruce Eton

278. **Telecobalt Treatment in Carcinoma of the Cervix.** (La telecobaltoterapia nel cervico-carcinoma uterino.)

By G. REMOTTI and M. A. FRANCINI. *Ann. Ostet. Ginec.*, **80**, 533. June 1958. 35 figs. 29 refs.

In a very long and detailed article the authors describe the treatment of six cases of cancer of the cervix.

The first three cases received telecobalt treatment alone, before proceeding to Wertheim-Meigs hysterectomy. The second three cases received radium, then telecobalt therapy and then were submitted to Wertheim-Meigs hysterectomy.

Careful pathological and histological examination of the specimens removed at operation was performed. It was found that nests of active malignant tissue were found in those receiving cobalt therapy alone. These areas were mostly at the site of the original growth. In cases receiving radium and cobalt therapy, no malignant cells were found.

They conclude that on histological grounds, treatment with a combination of radium and cobalt therapy is to be preferred. The ultimate conclusion must of course await the long-term clinical results.

Josephine Barnes

279. **Histological Findings in Cervices Amputated in Cases of Atypical Epithelium Observed at Colposcopy.** (Histologische Untersuchungsergebnisse an der obligatorisch amputierten Portio uteri bei kolposkopisch atypischem Epithel.)

By A. LEONHARDT. *Zbl. Gynäk.*, **81**, 736–744. May 9, 1959. 3 tables. 4 figs. 39 refs.

The author reports on a series of 6,012 patients first seen between 1956 and 1958. In 112 patients atypical epithelium or atypical blood vessels were seen and the cervix was therefore amputated as a routine. The series does not include cases of carcinoma recognized or suspected macroscopically. Histological examination of the 112 cervices revealed erosions in 34·7 per cent, atypical epithelium in 56·3 per cent and micro-carcinoma in 9 per cent (10 cases).

The author deprecates attempts at diagnosing cervical carcinoma by "hit-or-miss" biopsy, except for the purpose of confirming undoubted macroscopic findings. The whole of the squamo-columnar junction should be available for serial section.

Colposcopy makes it possible to select the cases in which amputation of the cervix can be justified.

Bruce Eton

280. **Prolapse and Cervical Cancer.** (Osservazioni sui rapporti fra carcinoma dell collo dell'utero e prolasso.)

By C. MOSSETTI and A. RUSSO. *Minerva ginec., Torino.* **10**, 785–788. Oct. 31, 1958. 4 tables. 27 refs.

It is commonly held that the association of carcinoma of the cervix with advanced degrees of prolapse is rare, many gynaecologists having seen at most a single case. It appears, however, that the association is not very uncommon in procidentia. Although the maximum age incidence of carcinoma of the cervix corresponds with that of third degree prolapse, among 449 cases of carcinoma at Turin (1949–57) none were found associated with this degree of prolapse (defined as where the cervix protrudes from the vulva without straining but the vagina is not inverted). On the other hand out of 41 women with procidentia four were suffering from cervical cancer. The authors consider that the immunity in third degree prolapse is explainable by the position of the cervix just outside the vulva, where it is protected both from irritating vaginal discharges and the rubbing of clothes to the latter of which it is subjected when further externalized.

W. C. Spackman

281. **Considerations in the Diagnosis and Treatment of Malignant Ovarian Tumours.** (Considerazioni sulla diagnosi e la terapia dei tumori dell'ovaio.)

By C. MOSSETTI. *Minerva ginec., Torino*, **10**, 874–882. Nov. 30, 1958. 9 tables. 39 refs.

In the past ten years 59 cases of malignant tumours of the ovary have been admitted to the Turin Clinic. Of these 39 occurred in women aged between 40 and 60. The chief symptoms complained of were pain in 46 per cent, and increase in girth or a feeling of tension or weight in the lower abdomen in 34 per cent. It was found that the most malignant cases gave the shortest history, in 60 per cent less than three months. Of tumours less than 20 cm. in diameter 70 per cent were innocent, but only 50 per cent of those larger than this. The diagnosis of malignancy was made pre-operatively in 64 per cent, at operation in 31 per cent and post-operatively in 5 per cent of cases. Pre-operative diagnosis of malignancy was facilitated by celioscopy and especially by cytokariology of ascitic fluid, in addition to the usual clinical and radiological signs.

Treatment was surgical, radiological, and by intraperitoneal injection of radioactive gold, the methods being used singly or in combination. The last of these forms of treatment gave some successes in advanced inoperable cases and it produced less general disturbance than roentgentherapy.

W. C. Spackman

282. **A Rare Case of Ovarian Arrhenoblastoma with Teratomatous Elements and Areas of Endometriosis.** (Raro caso di arrenoblastoma ovarico con aspetti teratomatosi e zone di endometriosi.)

By S. STEFANELLI. *Ann. Ostet. Ginec.*, **80**, 275. Mar. 1958. 9 figs. 11 refs.

A case is reported of a girl aged 17 who complained of amenorrhoea and symptoms and signs of virilism.

Abnormal hair had appeared and her voice had deepened. The clitoris was enlarged. A tumour was felt in the left ovary. The neutral 17-ketosteroid excretion was 24·1 mg. in 24 hours. Left salpingo-oöphorectomy was performed and a solid ovarian tumour was removed. Four days after the operation the 17-ketosteroid excretion was 11·65 mg. in 24 hours.

Examination of the tumour showed every variety of arrhenoblastoma, from the most immature, typically sarcomatous, forms to well-formed tubules. The latter were typical of the "testicular adenoma of Pick". In addition there were areas of teratomatous tissue, mucin-secreting glands and calcification. There were also some areas of endometriosis.

The patient remained well eight months after operation. The signs of virilism had regressed considerably, though not completely and regular menstruation had been re-established.

Josephine Barnes

283. **Combined Treatment of Ovarian Carcinoma.** (Kombinierte Behandlung des Ovarialkarzinoms.)

By D. Buttenberg and H. Lau. *Geburtsh. u. Frauenheilk.*, **19**, 308–325. Apr. 1959. 2 tables. 7 figs. 112 refs.

The methods used for treating carcinoma of the ovary in the Gynaecological Clinic, Heidelberg, are described in detail. In recent years intensive treatment using a combination of all available methods has been given to such patients. The treatment begins with bilateral oöphorectomy or removal of as much of the main tumour mass as possible. The uterus is not removed. Immediately after the operation 120 millicuries of radio-active colloidal gold are instilled into the peritoneal cavity. At the same time an intensive course of androgen therapy is begun by implanting 250 mg. of testosterone and this is maintained for the remainder of the patient's life by weekly injections of 100 mg. of testosterone. Eight or ten days after the operation an intra-uterine application of radioactive cobalt capsules or radium is made, to give a maximum dose of 4,000 r., as measured in the bladder and rectum (if necessary this is given in 2 doses). The patient is then discharged from hospital. Six weeks later the treatment is resumed either using deep X-irradiation through one field over the back and one over the front of the abdomen, to give a total surface dose of 6,000 r., or by using telecobalt to give a dose of 4,000–5,000 r. During this period of irradiation a second dose of radioactive colloidal gold is injected into the peritoneal cavity, and if necessary this is repeated again, but not more frequently than every three months.

The authors have tried to evaluate the objective palliation and the subjective improvement obtained in patients with incurable ovarian carcinoma treated by this intensive regime. An estimate of the 5-year cure rate has not yet been possible. From 1945–1950, 29 cases of stage III and IV carcinoma of the ovary (Latour classification) were treated by operative removal of the growth followed by a conventional course of X-irradiation of the abdomen. All these patients have since died. The average time of survival from the time of diagnosis was 10 months and only 3 patients survived for more than 30 months. Since 1954, 24 similar cases have been treated by the course of combined therapy described above. The average time of survival in this group was 13 months, but 19 patients are still alive and 5 of them are in good condition. It is concluded that the prolongation of the survival time obtained in these incurable cases was of value, particularly as the patients experienced a feeling of well-being.

[This article provides an excellent critical review of the latest operative and radiotherapeutic measures used in the treatment of carcinoma of the ovary, even if the regimen recommended by the authors is not acceptable to the reader.]

Peter J. Huntingford

284. **An Endocrine Basis for Endometrial Carcinoma.**

By A. I. Sherman and R. D. Woolf. *Amer. J. Obstet. Gynec.*, **77**, 233–242. Feb. 1959. 4 figs. 18 refs.

The authors examined ovaries from 133 patients operated on for endometrial cancer and compared them with ovaries from post-menopausal women who had no cancer. Hilar (Leydig) cell hyperplasia was present in 109 (82 per cent). In the control series of 86 cases hilar cells were present in 14. The patients with endometrial cancer had raised levels of LH secretion which fell to normal after bilateral oöphorectomy.

According to the authors' concept of the hormonal origin of endometrial cancer a female destined to develop that disease is endowed at birth with an abnormal complement of hilar cells which are responsive to LH. During the reproductive years these cells function at a minimum because of progesterone from successive corpora lutea. After the menopause this restraint is absent and so pituitary gonadotrophins are brought to bear fully on the abnormal hilar cells. These produce sexagens (any substance that may produce one or more of the basic triumvirate of effects of sex hormones be it androgenic, oestrogenic or progestational). These influence the endometrium adversely and cause the pituitary to excrete excessive amounts of LH in addition to the usual post-menopausal high FSH levels. The sexagens, being incapable of a feed back control on the pituitary gland allow excessive LH activity which causes hilar cell hypertrophy and ovarian stroma cell hyperplasia. Subsequently or concomitantly with the latter the endometrium becomes carcinomatous with independent biogenesis.

Thus by simply introducing into the body a hormone that might act by proper feed back control of the pituitary, the endocrine pattern might be interfered with. If this interruption were to occur before the time that this neoplasm becomes hormone independent it might inhibit the formation of endometrial cancer. Precedent for such feed back action on the pituitary is the well-known use of cortisone to inhibit ACTH production in the adrenal hyperplasia syndromes.

F. J. Browne

285. **Endometrial Carcinoma—Clinical and Histological Differences in Estimation of Stage, with Observa-**

tions on Appropriate Treatment. (Sui criteri di valutazione clinica e di terapia del cancro del corpo dell'utero.)

By C. MOSSETTI and F. VISCHI. *Minerva ginec., Torino*, **10**, 835–844. Nov. 15, 1958. 6 tables. 53 refs.

In a study of 154 cases of endometrial carcinoma seen at the Turin Clinic between 1949 and 1958 a marked difference was found between the clinical evaluation of the stage of involvement and that revealed after surgical intervention. Whereas by clinical appraisal in only 3·1 per cent did the tumour appear to extend beyond the uterus itself, histological examination in 114 cases operated upon revealed extension beyond the uterus in 18·1 per cent. The five-year survival rate of first stage cases treated only by radium was 60 per cent with no survival in later stages, whereas of surgically treated cases in stage I 81·8 per cent survived, and 50 per cent of those where the disease had extra-corporeal extension. Radioactive gold and other isotopes are used in this Clinic post-operatively in all cases where the disease is found to have spread beyond the uterine walls, with encouraging results.

W. C. Spackman

286. **The Association of Diabetes Mellitus and Carcinoma of the Endometrium.**

By J. B. VANDER. *Amer. J. Obstet. Gynec.*, **77**, 243–245. Feb. 1959. 3 tables. 9 refs.

Previously published figures have tended to show that endometrial cancer is more frequent in diabetics and this has caused speculation as to the possible role of the pituitary in the aetiology of cancer.

In the present study the number of patients who had endometrial cancer and also diabetes was determined and compared with the number of expected cases in comparable age groups of the general population. The incidence of diabetes in the 483 patients who had endometrial cancer was 5·6 per cent compared with the expected percentage of 5·4 which indicates that there is no significant difference. It is possible that the high incidence reported by previous observers is due to inclusion of a large percentage of patients whose only evidence of diabetes was a delayed glucose tolerance test.

F. J. Browne

287. **Histological and Histochemical Observations on Cases of Uterine Fibroids Associated with Adenocarcinoma of the Endometrium in Patients of Advanced Age.** (Osservazioni istopatologiche ed istochimiche su alcuni casi di fibromioma uterino associato ad adenocarcinoma endometriale in pazienti di eta avanzata.)

By M. A. FRANCINI. *Ann. Ostet. Ginec.*, **80**, 216. Mar. 1958. 20 figs. 47 refs.

This is a study of five cases of uterine fibroids associated with adenocarcinoma of the endometrium in women aged between 60 and 69.

The histological and histochemical changes are described. In all a surprising degree of rejuvenation of the uterus was observed, indicating oestrogenic stimulation of the uterus. The author is not able to identify the source of this oestrogen.

Josephine Barnes

288. **Adenoma of the Fallopian Tube.** (Il tumore adenomatoide della salpinge.)

By A. T. DEGNA and F. RILKE. *Ann. Ostet. Ginec.*, **80**, 495. May 1958. 5 figs. 36 refs.

A case is reported of adenoma of the Fallopian tube. This is a rare tumour and only 32 cases could be found in the literature.

This tumour occurred in a 44-year-old woman. Histological examination shows the features of an adenoma, but also muscle cells, endothelial cells and elastic tissue in the walls of the adenomatous tubules.

The question of the origin of these tumours is discussed. It has been variously suggested that they may come from Wolffian or Müllerian tissue, or from endothelium or mesothelium. An inflammatory origin has also been postulated.

Josephine Barnes

OPERATIONS

289. **Hysterosalpingography: A Survey of Some Opaque Media.**

By J. M. SHEACH. *J. Fac. Radiol.*, **10**, 103–107. Apr. 1959. 5 tables. 22 refs.

This is a survey of the results of using three different radio opaque media—Iodipamide (Biligrafin Forte: Endografin FL), Salpix and Diaginol Viscous.

A total of 181 examinations were made, using the different media in strict rotation. The clinical problem was largely infertility, but some examinations were for the diagnosis of pelvic swellings. A modified Everard Williams cannula and syringe were used under intermittent fluoroscopic control. Films were taken before and after injection and again 15 minutes later to estimate peritoneal spread; additional ones were occasionally taken. Each medium was compared with the others for radiographic opacity and viscosity. All were of equal radiographic opacity but Diaginol Viscous had the most satisfactory viscosity.

Complications such as pain, allergic phenomena, peritonitis, salpingitis and embolism were also investigated. Diaginol Viscous produced pain more often than Salpix, but less than Iodipamide; possible allergic phenomena (headaches, vomiting, etc.) were least with Diaginol Viscous. Peritonitis occurred once (with Iodipamide) and salpingitis twice, but in this case the type of medium was not specified. Embolism was not found at all.

The final view expressed was that although the ideal medium for hysterosalpingography has yet to be found Diaginol Viscous appears to be the most satisfactory available.

Robert Percival

290. **The Technique and Use of Urografin as a Contrast Medium in Hysterosalpingography.**

By R. W. MCNABB. *J. Fac. Radiol.*, **10**, 108–110. Apr. 1959. 2 tables. 6 figs. 9 refs.

The change to this medium was made in order to avoid the dangers of using an oily medium. Salpix was tried, but was abandoned because of technical injection difficulties. Viskiosol Six was highly satisfactory and was

used until it was withdrawn by the makers. Endografin had the great disadvantage of delayed pelvic pain. Urografin is a mixture of sodium and methylglucamine salts of N:N'-diacetyl-3:5-diamino-2:4:6-triodobenzoic acid. The strength used here was 76 per cent.

The radiographic density was satisfactory and absorption good, yet sufficiently delayed to determine peritoneal spreading (up to 90 minutes). Injection was done under direct screening using a soft rubber-coned cannula. A film was taken, the cannula removed, and the patient then walked about for ten minutes before the second film. As regards complications, in 181 hysterograms there were two instances of venous intravasation without effect, and pain was found only occasionally, other than in minimal degree. The conclusion was that Urografin is the most satisfactory medium yet used.

Robert Percival

291. **Posterior Colpotomy. A Practical Aid in Pelvic Diagnosis.**

By W. C. BRADBURY. *West. J. Surg. Obstet. Gynec.*, **67**, 55–60. Jan.–Feb. 1959. 21 refs. 2 figs.

The author presents the results of 407 colpotomies, 312 of them being preliminary to vaginal hysterectomy. Of the remaining 95, 54 were for suspected ectopic pregnancy, confirmation being obtained in 32 and no pathology being found in 5; the other 41 were done for other diagnostic problems, ovarian cysts being found in 23. The procedure appears to be safe, 5 (of the 95 cases) having some pelvic peritonitis and 1 other developing a pelvic abscess, 1 patient had some bleeding from the vaginal incision.

It is considered that the method has much to commend it providing the utero-sacral ligaments are not divided. In many cases it is possible to remove the affected tube through the vaginal incision.

[This would seem to be a useful procedure in cases of real doubt; it seems unlikely that it would need to be used as often as the author advocates.]

D. C. A. Bevis

292. **Follow-up Studies After Amputation and Conisation of the Cervix.** (Nachuntersuchungen nach Portioamputationen und Konisationen.)

By V. GRÜNBERGER and H. MARGREITER. *Zbl. Gynäk.*, **81**, 193–203. Feb. 7, 1959. 5 tables.

The authors report that at the Vienna University Clinic conization has lately taken the place of random biopsy. They review the cases of conization or amputation of the cervix carried out between 1955 and 1957. Of 224 patients asked to attend, 165 were seen and these form the material of this study.

In 106 cases a benign lesion was found on thorough histological examination although macroscopic, cytological, colposcopic or colpomicroscopic examination prior to operation had raised the suspicion of carcinoma in 73 instances.

Twenty-one patients were treated by conization, 30 by amputation and 55 by amputation at the time of colporrhaphy. Four patients were subsequently found to have uterine fibroids, 2 had metropathia, the menopause supervened in 8, abnormal uterine bleeding occurred in 18 patients, 6 complained of an increase in leucorrhoea although the cervix appeared to be normal, but in 14 (13 per cent) ectropion had developed around the new external os, which was treated with electro-coagulation. Three patients had a subsequent pregnancy and delivery.

Amongst 46 cases of pre-invasive carcinoma of the cervix the diagnosis was suspected on macroscopic examination in 24. In almost all remaining cases there were positive or suspect findings on colposcopic, colpomicroscopic or cytological examination. Treatment of these cases consisted in conization or amputation of the cervix and uterine curettage. If histological examination of the specimen showed a margin of healthy tissue beyond the carcinoma, no further action was taken. Otherwise hysterectomy was carried out.

In 13 cases histological examination after conization or amputation of the cervix revealed an invasive carcinoma. Eleven were treated by Wertheim's operation and 2 by radiotherapy.

Follow-up results are not yet available.

Bruce Eton

293. **The Technique of Synchronous (Two Team) Abdominoperineal Pelvic Exenteration.**

By H. E. SCHMITZ, R. L. SCHMITZ, C. J. SMITH and J. J. MOLITOR. *Surg. Gynec. Obstet.*, **108**, 351–356. Mar. 1959. 4 tables. 4 figs. 13 refs.

The authors have performed 68 pelvic exenterations 27 of which were done synchronously by 2 teams. These include anterior, posterior and total exenterations and in the great majority the indication was carcinoma of the cervix. Perineal excision is considered a necessary part of almost every exenteration whether partial or total. The impression has been gained that by means of the 2 team exenteration time and blood are saved, the tumour clearance is more adequate, the post-operative course is smoother and the mortality rate less.

Details and illustrations of the abdominal and perineal dissections are given. The authors favour the Bricker ileal conduit for urinary diversion after total exenteration. They create a "lid" over the brim of the pelvis of steel or tantalum mesh to prevent prolapse of small bowel into the pelvic cavity.

John P. Erskine

294. **Residual Urine and Its Importance in Timing Post-Operative X-Ray Therapy.** (Die Bedeutung des Restharn für den Zeitpunkt der postoperativen Röntgennachbestrahlung.)

By G. REIFFENSTUHL. *Zbl. Gynäk.*, **81**, 587–583. Apr. 11, 1959. 8 refs.

Cystitis after radical surgery for gynaecological cancer is attributed to trauma, interference with the blood supply, partial denervation predisposing to residual urine, and catheterization. An additional not uncommon cause is post-operative X-ray therapy.

In a study of 174 cases, the author observed a correlation between the occurrence of cystitis with pyrexia and the administration of X-ray treatment to patients with residual urine.

He emphasizes the importance of avoiding factors which predispose to urinary infection and points out that this is the third commonest cause of primary mortality following radical gynaecological surgery. X-ray therapy should be postponed within reasonable limits until the patient has no more residual urine. If it cannot be deferred, the author suggests as a compromise continuous bladder drainage except for temporary removal of the catheter during actual X-ray treatment.

Bruce Eton

UROLOGY

295. **Transurethral Bladder Neck Resection in the Female.**

By N. B. POWELL and E. B. POWELL. *J. Urol.*, **80**, 479–488. Dec. 1958. 10 tables. 5 figs. 21 refs.

Many female patients have bladder trouble which refuses to respond to treatment over a long period of time. Some of these patients require surgery. Indications for operation are residual urine greater than 3 ounces, recurring attacks of retention, recurring urinary tract infections, and failure of local treatment to give adequate relief.

The usual picture seen with the panendoscope is contracture of the bladder neck and granular masses forming a collarette at the vesical orifice or multiple polypi. Histological examination of the specimens removed revealed chronic inflammation with submucosal fibrosis and almost complete disappearance of the cavernous layer. Glands are frequently discovered, and in 5 cases glands with columnar mucous secreting epithelium, indistinguishable from that found in the prostate, were discovered. Polypi are always inflammatory.

Two hundred and fifty-four cases were treated. In 59 cases urinary cultures were negative, and in 37 there were abnormalities of the upper urinary tract. Results of treatment were as follows: 135 (55 per cent) cured; 33 (13·4 per cent) good; 56 (22·6 per cent) improved; 17 (6·9 per cent) poor.

J. H. Carver

296. **Drug Effect on the Female Bladder and Its Sphincter Mechanism.**

By A. F. YOUSSEF. *Obstet. Gynec.*, **13**, 61–73. Jan. 1959. 1 table. 8 figs. 78 refs.

Cystometry and sphincterometry were used by the author to study the effect of sex hormones and of drugs which act on the autonomic nervous system, on the urinary bladder and its sphincter mechanism under normal and pathological conditions.

Cholinergic drugs were found to increase the tone of the normal bladder and diminish the tone of the involuntary vesical sphincter, while adrenergic drugs had the opposite effect. The effect of anticholinergic and antiadrenergic drugs on the normal bladder was found to be much less pronounced.

Neither oestrogens nor androgens affected the involuntary sphincter tone, although oestrogens did elevate the bladder tone. On the other hand, the effect of hormones on the abnormal bladder and sphincter varied with the pathology present.

In cases of urethro-trigonitis symptomatic relief can be obtained temporarily by using anti-cholinergic drugs (Bellafoline and Buscopan). In some cases of bladder hypertonia simulating trigonitis the trouble is due to hyper-oestrinism and the engorgement is relieved when a period starts, and these can be treated with androgens. A feature of this condition is sometimes urge incontinence.

Patients with congenitally weak bladders can be successfully treated by anti-cholinergic drugs, although the treatment does not work if the trouble is psychogenic.

Some cases of bladder neck obstruction syndrome which commonly occur post-menopausally are due to hypo-oestrinism and a state of sympathetic hypertonia. Hydergine and oestrogen therapy cures such cases. In cases of post-menopausal urethro-trigonitis with sphincter weakness, the treatment should be a combination of oestrogen and androgen. A similar combined treatment is effective in cases of sphincter weakness after the menopause where there is no prolapse.

J. G. Dumoulin

297. **The Contribution of Sphincterometry to the Diagnosis of Urinary Incontinence in the Human Female.** (Contribution à l'étude du diagnostic de l'incontinence d'urine chez la femme par la sphincterométrie.)

By C. BALLERIO. *Gynéc. prat.*, **9**, 222–230. 1958. 4 figs. 20 refs.

Sphincterometry has been used by the author as a means of investigating urinary incontinence in the female. The instrument used consists basically of a mercury manometer connected to an olive-type cannula. The author has also produced a special compact instrument in which an anaeroid manometer is used which he claims is more convenient in practice.

In use, the tip of the cannula is inserted into the external urethral meatus, the bladder having been emptied by catheterization. The patient is now asked to relax and air is pumped into the circuit. The pressure reading will be found to mount and then suddenly to fall. Coincident with the fall in pressure, the noise of air passing into the bladder can be heard. The highest reading achieved indicates the competence of the involuntary sphincter mechanism of the bladder. After a rest of two to three minutes the procedure is repeated with the patient contracting her pelvic muscles as firmly as possible in an effort to "hold back her urine". The reading obtained is taken as an index of the power of the voluntary sphincter.

The author has shown in some five hundred cases that whereas in the normal woman the power of the voluntary muscle always exceeds that of the involuntary

mechanism, the reverse is true in those with stress incontinence.

Successful operation repair for stress incontinence always results in a restoration of the values to their normal relationship, but unsuccessful repair does not do so even though the clinical and cystographic pictures may be completely normal.

[This is an interesting paper, dealing as it does with a method of investigation which has hitherto been described almost exclusively in the German literature and which has received scant attention in the United Kingdom.]

H. G. Dixon

298. **The Diagnosis of Urinary Incontinence.** (Zur Diagnostik bei Harninkontinez.)

By H. GLEICHAUF. *Zbl. Gynäk.*, **81**, 237–250. Feb. 14, 1959. 5 tables. 1 fig. 52 refs.

The assessment of stress incontinence may at times be difficult, particularly as even unmarried healthy young nulliparous women will often admit to relative stress incontinence, for instance, when laughing. Failure to cure stress incontinence is often due to insufficient preliminary investigation and inaccurate diagnosis. The author reports on the study of an unselected series of 42 patients complaining of relative urinary incontinence, with or without prolapse.

Diagnostic methods included inspection, palpation, cystoscopy in certain cases, cysto-urethrography and sphincterometry. The latter investigation determines the changes in sphincteric pressure at rest and on voluntary contraction.

Criteria suggestive of true incontinence were established on the basis of difference in sphincteric pressure; the mode of descent and the appearances of the posterior vesico-urethral angle observed with oblique radiography.

In 20 per cent of all patients suffering from stress incontinence, none of the criteria was present. In over half of the cases there was none, or at most one, criterion. Criteria obtainable by all three methods were present in only 10 per cent.

The author concludes that great care has therefore to be taken in deciding with these methods whether relative urinary incontinence is genuinely present.

Bruce Eton

299. **Pseudodysuria in Young Girls.** (La pseudo-dysurie chez les fillettes.)

By R. PETER. *Gynéc. prat.*, **9**, 215–220. 1958.

Pathological states of the vulva can give rise to pain during or after the act of micturition. As this symptom is not associated with any lesion of the urinary tract under these circumstances, it is better known as pseudo-dysuria. It is more common in the female before the menarche than true dysuria and much urinary tract investigation could be avoided by more thorough gynaecological examination. The principal causes are:

(*a*) Vulval trauma, especially that associated with masturbation.

(*b*) Adhesions of the labia minora, especially of the anterior parts of the labia.

(*c*) Vulvitis, associated either with faulty hygiene, oxyuriasis or gonorrhoea. Monilial infection gives rise to pseudo-dysuria when associated with a secondary bacterial infection. Trichomonas infection can cause the symptom in its own right, but it is rare in the pre-pubertal girl.

(*d*) Vaginitis, with a purulent discharge. The author points out that pseudo-dysuria is not associated with a vaginitis due to a retained foreign body. He feels that this is because there is no vulvitis associated.

He makes special reference to prolapse of the urethra, pointing out that the pain here is a true dysuria, although because of mistaken diagnosis the patients usually come under the care of a gynaecologist.

No references are quoted in the article.

H. G. Dixon

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